Eureka and the Art of Discovery

A Guide for the Curious, the Creative and those who have No Talent at all

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Anyone can Be a Discoverer

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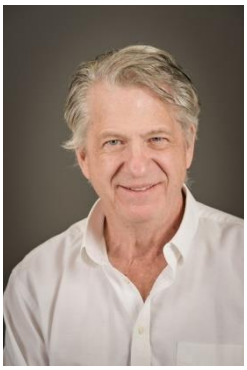
About the Author



Dr Richard (‘Rick’) J Johnson is a physician and scientist who has been in love with discovery all of his life. While highly cited in the scientific community, he has also published several books for the general reader, including *The Sugar Fix* (Rodale, 2008), *The Fat Switch* (Mercola.com, 2012) and *Nature Wants Us to Be Fat* (Ben Bella Books, 2022). A clinician boarded in Internal Medicine, Nephrology and Infectious Diseases, he is also the founding editor of a major textbook on kidney disease (Comprehensive Clinical Nephrology). He is especially known for his research on sugar and obesity. Here he discusses the joy as well as art of discovery, focusing on breakthroughs on medicine, but of relevance to those interested in creativity, invention, and art. He lives in Aurora, Colorado with his wife, Olga, children Tracy and Ricky, and with two irresistible dogs, Apollo 11 and Charlie Brown.

About the Artist

Zach Thrun has been a professional artist and creative technologist for over 20 years. His work includes fine art, video games, illustration, interactive, and motion-picture media. He has long loved cartoons and comics and injects humor and levity into his life and work wherever there is an opportunity.

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***Key Message**: When things are not progressing, what should you do? When do you persevere, and when do you change directions? Do you take the risk and study something that you are not an expert in, or stay with what you are most familiar with? Follow your instincts. If your research takes you out of your discipline, be brave. If you find yourself on a "new road", try to bring in experts to help you if it is a topic for which you do not have a lot of knowledge.*

Chapter 6 The Trick is to Overcome the Barriers…

Why does science fail us? Why do amateurs have advantages over experts? It is time to visit Sherlock Holmes.

Chapter 7 so you can Make a Discovery …

The discovery process is enhanced by being open to possibility, challenging what you have learned, reading outside your field, and practice making analogies. This chapter provides vignettes/stories to illustrate these key points.

Chapter 8 Prove the Discovery is Real…

While inductive reasoning identifies the hypothesis, is deductive reasoning is usually required to prove it. The classic approach involves the Clinical Trial and Scientific Method, but proving by anecdote is powerful and memorable, but while convincing, can also be dangerous. Among the trials and tribulations, look for the Golden Goose but beware the Black Swan.

Chapter 9 …and Get the Discovery Accepted

Discoveries can be lost as easily as they are made; it is therefore critical to make the discovery known to the world. How do you convince the experts who for decades have viewed things differently, or do you have to wait for them to die out and for a new generation that is more open to your idea?

Chapter 10 A Personal Story: In Search of King Priam's Treasure

The last century saw an epidemic rise in obesity, diabetes and many other "non-communicable diseases". What if there was a single, primary cause? My personal story in search of King Priam's treasure.

Chapter 11 The Exhilaration of Discovery and Why Being a Discoverer Matters

On the joy of discovery and why it will not make you famous or rich, but it will make you happy.

Acknowledgements

Bibliography

Illustrations ***by Zachary Thrun***

Foreword by Richard Rossi

Every child is born an artist, an actor, and a scientist, imbued with an insatiable curiosity that can drive their parents to distraction. It's a wondrous thing to behold. But then society and our education system beat those traits out of us and pushed us to suppress our questioning of accepted dogma and conform to a more conventional way of thinking. *Eureka, the Exhilarating Quest of Discovery* by Dr. Richard Johnson is a wonderful book that encourages you to hold tightly to your natural sense of awe and curiosity about the world around you. While Johnson's book primarily focuses on discoveries related to health and medicine, the book is relevant to anyone who has an interest in creativity and discovery.

How can curiosity be unleashed? Dr. Johnson shows us how history's greatest thinkers and explorers succeeded because they refused to let go of their insatiable curiosities. They looked at observations that contradicted mainstream beliefs and courageously asked, "What if...". They embraced ideas that initially seemed outlandish or absurd. By nurturing that questioning mindset, these visionaries unleashed powerful new understandings about our universe.

Throughout the book, Johnson's storytelling introduces readers to the transformative scientists, inventors, artists, and scholars who exemplified this intellectually irreverent approach. He illustrates how their open-mindedness empowered them to capitalize on unexpected, serendipitous occurrences in ways the closed-minded couldn't perceive.

While lucky breaks undoubtedly supercharged many breakthroughs, it was these pioneers' unique mindsets that allowed them to recognize the deeper significance of seemingly random events and forge new paths of inquiry. The unifying thread connecting all of these revolutionary discoverers was their shared ability to never lose touch with their innately inquisitive nature. They retained the "beginner's mind" curiosity to keep asking audacious "What if?" questions without limitations—the same unwavering questioning spirit we observed in ourselves as children before insecurities and societal pressures crippled our imagination. By nurturing that sense of wonder about our infinite universe's complexities, these innovative trailblazers shattered calcified assumptions and dramatically expanded humanity's horizons.

Johnson compellingly argues that each of us can rediscover and cultivate that same curiosity-driven mindset to unlock new creative and intellectual breakthroughs, no matter how big or small. He champions the perseverance and resilience to keep pursuing unorthodox ideas in the face of resistance and setbacks. He emphasizes an open-mindedness unconstrained by ego or

dogma, combined with a reciprocal humility to adjust personal hypotheses when confronted with compelling new evidence. He highlights an intrepid risk tolerance for challenging institutional orthodoxies when unexplained contradictions arise.

Above all, he encourages a willingness to imaginatively explore any intellectually tantalizing "What if?" no matter how outlandish or unconventional it may seem at first glance. The author's autobiographical stories of his own investigations pursuing unexpected leads make these principles come alive in engaging ways. We see how his scientific breakthroughs sparked from doggedly following curiosities outside his specialties into uncharted terrain. Like the legendary discoverers profiled, Johnson's path was marked by dead-ends and course corrections driven by new observations and insights.

These personal tales underscore how our most revelatory understandings don't emerge from accepted knowledge but from fearlessly questioning it. Ultimately, *The Art of Discovery* leaves readers feeling profoundly inspired about the infinite underexplored creative and intellectual frontiers awaiting anyone intrepid enough to think differently.

Johnson reignites our forgotten senses of childlike wonderment about the vast mysteries of our cosmos that remain to be unlocked simply by embracing an attitude of humility, irreverence, and bold questioning when confronted with the unknown. We're reminded that revolutionary ideas are not conceived through genuflecting to conventional wisdom but by daring to view the world through fresh, imaginative, unshackled perspectives as beginners again.

With Johnson's warm yet impassioned encouragement, we're left feeling empowered to discard crippling insecurities about challenging established beliefs. We're liberated to conceive even seemingly impossible ideas and tenaciously pursue the inquisitive threads beckoning us into unmapped conceptual landscapes.

The most profound discoveries throughout history have arrived not through conformity but from open-mindedness and curiosity defying limitations. Those marvelous new vistas await anyone courageous enough to embrace *Eiureka's* spirit.

Richard Rossi
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Prologue: The Art of Discovery

When I was five years old, I wanted to be an archeologist. Mind you, I could not pronounce archeology correctly as early in my life I had trouble pronouncing "r" (which is a significant problem if there is an R in your name) as well as "l". The reason I wanted to be an "awkeowogist" was not because I had any idea what they actually do, but because I wanted to find treasure. In particular, pirate treasure.

When I was young, my family would sometimes travel to Florida, where we stayed in Boca Grande, a town on Gasparilla island. Gasparilla is an island off the southwest coast that was named in honor of José Gaspar, the legendary Spanish pirate from the 18th century who plundered ships and amassed a great fortune. Rather than be captured by the U.S. Navy, it is said that he jumped off his ship to his death. According to local legend, he buried his treasure on Gasparilla Island. However, the treasure has not been found.

As a boy, I would walk the beach of Gasparilla island right after a storm, claiming to be looking for cool-looking seashells, but in actuality, I was secretly looking for a washed up gold doubloon. I imagined I'd find a wooden chest shackled with irons and surrounded by skeletons, which would be marked by a black flag bearing a skull and crossbones. Inside the chest, on top of the heaps of gold coins, would be a letter written by José Gaspar himself, congratulating me on the find! (I had a very active imagination.)

Even though I never found José Gaspar's treasure, the idea to become an archeologist stayed with me.

I read about the discovery of Troy by Heinrich Schliemann, and how he found King Priam's treasure (although we now know it was from a different time period in the history of Troy).

I learned how Hiram Bingham, a lecturer in history at Yale, organized an expedition in Peru that led him to the ancient city of Macchu Picchu. While Bingham was not the original discoverer of Macchu Picchu (whose local name was Huayna Picchu), he was the one who made the discovery of Macchu Picchu known to the world.

It will surprise no one that I went on to major in anthropology, with a focus on archeology. Unfortunately, once I found out what the field of archeology was really about, my dream of finding big treasures eased away. But it turns out the world is full of treasure waiting to be discovered.

During my time in college, I found that I liked science—especially biology. My father, who was an academic physician, encouraged me to go to medical school. So I decided to take the

medical school entrance exam just to see how I would do, and when I got back my scores I realized that medical school was probably where I should go. I have never regretted that decision.

For over 40 years I have devoted myself to the field of medicine. But I never forgot my love of discovery. I realized that to most effectively treat a patient, one needs to have the correct diagnosis of what that individual suffers from. In turn, diagnosis requires piecing together clues based on taking a "history" of the illness, looking for clues on the physical examination, and obtaining critical laboratory work and imaging studies.

Shortly after starting my medical residency I realized that there was more to medical discovery than simply diagnosing the disease, for so often the cause of the disease was not known. Yes, doctors are great at giving complicated names to diseases and once you carry that diagnosis, there are the standard treatments given. But often we do not actually know what causes the disease. This carries over to many of the more common diseases that affect humankind, such as obesity, high blood pressure, diabetes and Alzheimer's disease. If we could discover the cause, it would be much easier to find the cure.

So I decided that, while I wanted to continue to take care of patients and practice the art of medicine, there was an opportunity to go into medical research to see if I could help uncover the causes of diseases, or identify new treatments.

Over the years I have experienced both successes and failures, and many lessons learned along the way. The most important of which is that the art of discovery does not require genius or unusual expertise. Rather, discovery essentially requires curiosity and passion.

While the "science" of discoveries is well discussed, there is not much written about the "art" of discovery. This is especially true in the medical profession—for doctors spend hours learning the science, but almost nothing about how to discover things. Indeed, there is a new wave of medicine that actually teaches away from discovery.

Many young doctors now rely heavily on data collection that is assembled into "scoring systems" that are then used to direct treatment. One might get a score for how severe one's liver disease is, or a score to guide what type of treatment should be done after having a heart attack. Experts have assembled treatment guidelines based on clinical studies ('evidence-based' medicine). These scoring systems and guidelines allow for consistent clinical care that is state of the art and often results in improved outcomes. These scoring systems will become even easier

with the advent of artificial intelligence, for all we will have to do is follow the directions of what is told to us!

But there is a price, in that it takes away thinking, curiosity, and passion, which are at the heart of the discovery process. If one simply follows an algorithm on a paper, one does not have to think at all, and hence might miss clues that give insights into how or why the disease developed.

While the book is primarily about discoveries in health, nutrition and disease, it should be relevant to anyone interested in the the art of discovery. And there is a need for this type of book. Afterall, we have hundreds of books each year focusing on diet, nutrition and exercise that are aimed at improving our physical and mental health, books on how to make money and enjoy financial success, books on assisting our emotional health, including the power of kindness and giving. These books provide a lot of great advice, and I am one of many authors that have written on these topics. However, there is more to life than just being happy, it would also be great to find meaning in life. Discovering something that might help others is at least one way this can be done.

If there has ever been a time the world needs to stimulate discovery, it is now. There are so many ongoing issues of world concern, such as climate change, dwindling natural resources, and environmental pollution that require new approaches and solutions. And it is my belief that all of these problems have solutions, and that we are well capable of finding them. Indeed, my life-long work gives me immense hope and optimism for the future. One of the most powerful ways to learn is from nature itself, as over millions of years many animals have adapted or evolved to protect themselves from extreme changes in the environment. We can gain from Nature's eons of experience. Studying how nature adapts (biomimicry) to stressful situations is giving insights into prevention and treatment of cancer, protection from heat and radiation, and more.

The purpose of this book is to highlight the beauty of the discovery process. While the emphasis is on medical discovery, it carries over to all fields, and the processes described can also help individuals who want to stimulate their creativity. This includes bringing out the artist in an individual, encouraging the thought processes that can lead to new inventions, and the benefit of keeping oneself open to new ideas and approaches.

Chapter 1 It Begins with an Observation

Sherlock Holmes turned to Dr Watson and remarked, "Now what did you gather from that woman's appearance? Describe it."

"Well she had a slate-coloured, broad-brimmed straw hat, with a feather of brickish red. Her jacket was black, with black beads sewn upon it, and a fringe of little black jet ornaments. Her dress was brown, rather darker than coffee colour, with a little purple plush at the neck and sleeves. Her gloves were greyish, and were worn through at the right forefinger. Her boots I did not observe. She had small round, hanging gold earrings, and a general air of being well to do, in a vulgar, comfortable, easy-going way."

Sherlock Holmes clapped his hands softly together and chuckled.

" 'Pon my word. Watson, you are coming along wonderfully. You have really done well indeed. It is true that you have missed everything of importance, but you have hit upon the method, and you have a quick eye for colour."

A Case of Identity, in the Adventures of Sherlock Holmes, by A. Conan Doyle, The Strand Magazine, 1891

* * * *

"I understand that there is an American medical student who is in the room. Could he please come forward and introduce himself?"

Sweat formed on my brow and I cringed. I had only been in London a week, and this was just the second day on my three-month medical rotation at the Hammersmith hospital, which was the main medical center for the Royal Postgraduate Medical School. As a third-year medical student at the University of Minnesota, I'd had the opportunity to study abroad. I was excited to do this, as I had never travelled outside of the United States, and this was a great opportunity to see medicine practiced at one of the most famous institutions in the world.

The British like titles, but Professor Keith Peters had more than most. His official title is Sir David Keith Peters GBE FRS FMedSci FRCP FRCPE FRCPath FLSW[1]. Once a week, he would come to the ward and go on medical rounds.

[1] Later in my career I had a chance to meet Sir Keith Peters in a social setting, and I can state he was quite an enjoyable character. In retrospect I think it was his title that scared me the most on that first day.

Not surprisingly, his "rounds" were a big deal. The consultants (the British name for the attending physicians) would show up in their best dress and the registrars (the British name for medical residents) would prepare their presentations. The medical students would assemble and the nurses would pull the charts. Even the patients were told to be ready for when the great professor would come by.

The ward was in the old style, a very large room with rows of beds. Rounds would proceed from bed to bed, with the professor surrounded by the consultants, the registrars, the students, and the nurses. I, being new and unexperienced, decided to stand behind the huddle of medical students so as to be least conspicuous.

When Professor Peters showed up in his white coat, the rounds began. The consultant took him to a specific bed where the patient would be sitting and waiting for him. The registrar then presented a brief history of the illness, and Dr. Peters asked the patient various questions. He then would make some erudite comments, everyone would nod in agreement, and we would then move on to the next bed.

The problem came when Dr. Peters went to the bed of the third patient. Rather than waiting for the registrar to speak, he turned to the medical students and asked if there was an American medical student present.

When I heard those words, I looked at the other medical students, hoping, just hoping, that one of them was also from the United States. No such luck, and so I nervously stepped forward.

"Johnson, Richard Johnson is my name, sir. Yes, I am a medical student from the University of Minnesota, sir."

He asked me to examine the patient's neck.

I looked over at the patient who was sitting on the bed, wide-eyed like me as if he was also surprised at this request. He had a huge lump on his neck, in the midline, right where the thyroid is located. I asked the patient his permission, and then felt the lump. I turned to Professor Peters, "I believe it is a goiter, sir."

"Do you call that an examination?" Before I could answer, he said, "Let me show you how this is done. You begin by inspection." He then tilted the head of the patient with his hand, and shined a flashlight. "It is important to look at the location of the mass, whether there are skin changes overlying it, and to determine its size."

"Next one must perform percussion, to see if it is hollow or solid." He placed one finger over the lump and lightly tapped it. I could barely hear anything. "In this case it is solid."

"You next perform auscultation, to hear if there is any significant blood flow, such as a bruit[2]. This can occur with Grave's disease." He placed the stethoscope over the lump and listened for a few seconds. "In this case, there is no bruit."

The more he talked, the smaller I felt.

"Then you have to palpate the mass. The mass is 3 centimeters in height with a width of 4 centimeters."

The patient, who did not seem to know he had a mass, stared blankly.

"Then you need to see if it is bound to the underlying tissues, or if it is mobile, and we need to determine it is affected by swallowing." He turned to a medical student who apparently knew this was going to be said and already had a glass of water for the patient to swallow.

The patient swallowed some water as the Professor palpated the neck.

"In this case, the mass is mobile. It moves when he swallows."

Every time he said "mass" I looked to see the patient's reaction. But it remained the same, wide-eyed in mystification.

"But we are not done. We do not consider just one diagnosis, but rather we need to provide a full differential. For example, it could be a thyroglossal cyst, thyroid carcinoma, medullary cancer of the thyroid, brachiocephalic cyst, an enlarged lymph node, …"

Everyone was nodding. I nodded as well.

"But in this case, you were right," he said with a sigh. "It is a goiter." He turned to one of the consultants. "On to the next case." And I slid back to where the medical students were, some of whom were quietly snickering.

While I was initially embarrassed, I realized that I was lucky to have had this experience, and it made me realize that I wanted to improve my clinical skills. I began to think about Sherlock Holmes. The author of the Sherlock Holmes tale, Sir Arthur Conan Doyle, was a doctor himself, and he based the Sherlock Holmes character on a professor from his medical school in Edinburgh, the surgeon Joseph Bell who apparently was uncanny in making diagnoses of patients presenting with unusual symptoms or physical signs. This made me think that, if I mastered the ability of

[2] A bruit is an abnormal sound, often synchronous with the heartbeat, that can be due to high blood flow within the tissues.

taking a history and physical examination, I might become great at diagnosing even the rarest of diseases.

An inspiring moment occurred the following week, when I spent a day in the cardiac ward. I was just entering the ward, when the famed cardiologist, Professor Celia M Oakley, rushed by me. Oakley was known for her incredible ability to diagnose practically any heart condition by simply listening with her stethoscope. When I got to the ward, there was a lot of activity as the nurses and registrars were preparing to take one of the patients directly to the 'theater' (the British name for operating room). Professor Oakley had noted a subtle change in a murmur that told her that a patient with an infected aortic valve had a pending rupture of the valve into the pericardial space. Her skills were so good that an echocardiogram was not needed.

As for me, I was not such a great diagnostician.

That I am not good at observation was really homed in with a trick my father did to me once. He took a urinalysis cup that contained his own urine and showed it to me. "Rick, in medicine the power of observation is key. For example, take this urine sample. You can put it up to the light to look for its clarity; if it is cloudy it may signify infection. Take a look at the color--- if it is red, it may signify blood or the breakdown of muscle while if it is brown it may contain bilirubin such as from a person with liver disease. You can also smell it (he took off the lid and took a deep sniff), for example, to smell the pungent odor of acetone that occurs in the person with diabetes that is poorly controlled. You can also taste it (and as he said this, he dipped one of his fingers into the urine and then put it in his mouth) to see if you can taste the sweet flavor of glucose that is present in diabetes."[3]

I gave my father a disgusting look. "Did you actually taste your own urine?"

My father winked. "No, you just need to improve on your observation. Look again." My father then took his middle finger and dipped it into the urine, but as he raised his hand he switched it up so that it was his index finger that he put in his mouth.

So over the years I realized that I will never have the skills of Sherlock Holmes, and that there are many clinicians in this world who see more than I do. In fact, I have come to the realization that I am not that great an observer, even when I am not working as a doctor. I rarely

[3] This may not sound so crazy as back in the 1600s a Liverpool physician, Mathew Dobson, boiled 2 liters of urine from a diabetic subject to generate a brownish powder that "smelt sweet, like brown sugar, and could not be distinguished from sugar, except that the sweetness left a slight sense of coolness on the palate."

notice new buildings that have been constructed even if they are on my way to work, or when my wife puts up a new painting or gets new furniture for our home. In fact, even as a child my favorite pastime was dreaming. I like to look out windows and see nothing at all except my imagination. So one might think that I would be lousy at discovering things. And perhaps I am not that good at it.

But the wonderful thing is that you do not have to be like Sherlock Holmes and see what no one else sees. For most discoveries, the observation is evident to everyone. However, the key is to act on it. Winston Churchill captured this idea with his quote "Men occasionally stumble over the truth, but most of them pick themselves up and hurry off as if nothing ever happened." And while he was talking about truth, it is equally true for observations.

So let's investigate how making a simple observation can lead to a discovery!

The Discovery of the First Diuretic

One of the most desperate situations in medicine, especially in the past, occurred when a person retains fluid. For centuries the condition was called the dropsy, and often had an innocent beginning and a horrible end. The earliest sign is a slight swelling of the ankles that one may not notice until the socks are removed, leaving a telltale indentation in the skin. But whereas this can be normal in individuals who stand most of the day, in some unfortunate individuals the swelling heralds worse things to come. Water and salt continue to accumulate, causing the weight to increase daily. The feet swell such that the shoes no longer fit, the hands swell such that the rings become tight and have to be removed. The water marches up the leg, tightening the skin to a fine shiny sheath that can break down leaving sores that can become infected. The leg is so water-logged that even the slightest pressure of a finger leaves a depression that can hold a marble, and the legs become heavy such that one can barely walk. The days are marked by the great exertion it takes to walk with the legs swollen, heavy and numb.

As the legs swell, the abdomen becomes increasingly taut, and the belly inflates like a water balloon, leaving the individual bloated and water-logged, heavy and helpless. In some cases the faces become so puffy that the eyes are almost swollen shut. As the author Samuel Johnson (1709-1784) wrote, "A dropsy gains ground upon me; my legs and thighs are much swollen with water, which I should be content if I could keep it there, but I am afraid it will soon be higher". Indeed, the worst is when the water accumulates in the lungs, causing difficulty to breathe. One can hear

the water in the lungs with the stethoscope, sounding like the distant rustling of leaves in the rain. Sleeping at night is a haunting experience, for the individual may wake up gasping for air, being forced to sit up in bed to catch his breath. Eventually one succumbs from suffocation, heart attack or infection. Such was the destiny for those with the dropsy.

Regardless of what type of dropsy it might be, the primary treatment was the same—to find a way to rid the excess salt and water. For centuries different treatments had been tried, from removing blood by bloodletting or by leeches, by draining the fluid from the swollen bellies, or by the administration of laxatives. However, the dream would be to find a 'diuretic', a pill or injection that causes the person to urinate the excess fluid. Some concoctions had been found to occasionally increase the amount of urine, such as the powdered bulb of Squill (a plant) or a chemical extract obtained from tea. Sadly, nothing worked consistently, and there was a great need for an effective diuretic that could curb this miserable disease.

It was October 1919, and almost a year since the fall of the Austrian-Hungary Empire. Vienna was stricken with extremely high inflation and a serious shortage of food and clothing. Starvation and sickness were common, especially among children. But when medical care was needed, there remained the University of Vienna and the First Medical University Clinic, also known as the Wenckebach Clinic to honor the Chairman of Medicine, Karel Frederik Wenckebach. Wenckebach was a famous cardiologist, and helped establish the clinic as one of the earliest and most important cardiology centers in the world. He also was known to give some of the most boring lectures in the world that tended to put the medical students to sleep except for those forced to sit in the front row.

The discovery of one of the first effective diuretics was from one of those medical students. Alfred Vogl, a third year medical student relatively new to the wards, was still on a steep learning curve. That afternoon his team admitted a young girl named Johanna with diarrhea and vomiting. She was thin and chronically ill, as she had been born with congenital syphilis. Syphilis was widespread at the time, and likely had been brought to Europe centuries before by members of one of Columbus's expeditions to the Americas.

A horrible disease, it initially manifests as sores on the genitals, but then disappears leaving the individual to falsely assume that the infection had resolved. Sadly, the infection continues to fester inside, only to present years later, with numbness, loss of coordination and ability to walk, with dementia, or sometimes with large aortic aneurysms and heart disease. During pregnancy, the

infection could pass from the mother to the baby, resulting in bone abnormalities, deafness, and other problems. Syphilis could be treated by injections with mercury salts, but treatment had to be given for years and was not very effective. Indeed, there was a saying, alluding to the Roman gods, that "one night with Venus is followed by seven years with Mercury." While a newer drug known as Salvarsan (an arsenic-based compound) had been recently developed that was thought to be more effective than the toxic mercury-based compounds, that was not available on this particular admission.

Each day, the Attending Physician would go on morning rounds of the hospitalized patients with the students and nurses, where he would take brief histories and examine the patients, teach the students, and make sure that the correct treatments were initiated. When the Attending Physician reached Johanna, he explained how congenital syphilis was hard to treat but he told Vogl that he should still order some mercury salts for injection.

A few days later the Attending Physician was again seeing patients on morning rounds, but, when he got to Johanna's bed, he learned that she had not been treated. Vogl, under fire, was asked to find out why this had not happened and to make sure she would get treatment immediately. After rounds, Vogl called the pharmacy only to find out that he had made a mistake and had ordered the mercury salt in water, whereas it needed to be in oil. When he learned that it would take the pharmacy several days to get the new order ready, he became quite distressed, as he did not want to incur any more anger from the Attending.

As Vogl hung up the phone, he was approached by an older man who had overheard the conversation and could see that Vogl was quite worried. He introduced himself as Raszowsky, and told Vogl he had been an army surgeon for the Austrian-Hungary army, but had lost his job with the dissolution of the army. Unemployed, he spent much of his time hanging out in medical clinics as an observer, but always with the hope that he might find another position. He reached into his pocket and produced a small box, and said, "Perhaps you can use this. It is a new mercurial drug known as Novasurol." He placed it in Vogl's hand, and gave a sad smile, "I have no use for it anyway, as I no longer have any patients."

Vogl, afraid to wait any longer, agreed, and gave an injection to Johanna later that day. The next morning he went to see her and reviewed the vitals and other records that had been made by the nurses overnight. While the nurses had recorded the temperature and vital signs, they had also recorded the amount of urine that was produced. As he reviewed the nursing records, he discovered

that Johanna had urinated almost three times her normal amount, which represented about 5 cups (1200 cc). This seemed unusual to him, and so he kept an eye on the daily urine output and how it related to the administration of the drug, which was given two more times, every other day. He noticed that the urine volume always increased on the night following each injection, amounting to roughly 6 to 8 cups of urine. Realizing that the new mercurial might be acting as a diuretic, he told his attending, only for the attending to respond that this was likely a normal variation in biological rhythms and that it meant nothing.

After a few days, Vogl resumed the injections, each time observing an increase in urine in the subsequent hours. Vogl began to wonder whether the effect of Novasurol to increase urine might be observed in another patient with syphilis. At that very time there was an old cab driver on the ward with syphilitic heart disease, with significant heart failure and swelling of his legs. Vogl injected the man with Novasurol, and noted to his amazement that the patient passed over 40 cups (10 liters) of urine that night. Now the Attending became excited. A few days later, a boy was admitted with severe heart failure from rheumatic heart disease. He had massive swelling (edema) and was making almost no urine, and importantly, he did not have syphilis. Although near death, he was given an injection of Novasurol. Within minutes, he began urinating, generating about 3 L before he succumbed to the heart failure.

And so it was that the first effective diuretic was identified. It became the primary means for treating heart failure and edema until the 1950s when the thiazides diuretics were introduced. Interestingly, Vogl left the clinic in January 1920 to continue his training in Berlin, and it was his attending (P Saxl) and the medical student who replaced Vogl (R Heilig) who were to report the discovery in the literature.

There are several important aspects related to this discovery. First, it began with the observation by a medical student that the drug caused a marked increase in urine output. He confirmed his finding by observing this change after each injection of the drug, and then he presented his finding to the attending. However, the observation was discarded by the attending who attributed the finding to normal variation, and in so doing the attending, who was supposed to be the expert, effectively "closed the book", blocking his ability to see what was actually happening. He also likely did not view the finding as important as fluid retention was not a problem for the patient. However, Vogl continued to be bothered by the observation and had the insight that the drug might be beneficial, which he then "tested" by giving the drug to a patient

with syphilis who also had fluid retention from heart failure. Only when Vogl noted a dramatic production of 10 liters of urine did the attending notice. Then, ironically, the attending ended up writing the paper and claiming the credit.

The take-home message is that discovery often begins with an observation that the individual cannot forget. In this case the observation was relatively blatant and did not require the sleuth of Sherlock Holmes. It also did not require an expert, and in fact the expert did not see the potential impact of the discovery until the medical student confirmed his suspicion by giving the mercury-containing drug to another patient. And then the attending takes all of the credit, which also occurs a little too often!

But importantly, discovery often begins with an observation. Let me share with you a personal example.

How an Alaskan Fisherman helped Identify the Cause of a Mysterious Kidney Disease

While I trained as a physician in internal medicine, I also completed a specialty in kidney disease at the University of Washington in Seattle. There I became an attending physician, spending some of my time in clinic where I would see patients with various kidney diseases, and the rest of the time I worked in the laboratory, where I performed research to better understand kidney diseases. I did my training in the laboratory of Dr William Couser, who was both a brilliant physician and a great mentor. It was while working in his laboratory that I met a Japanese physician and scientist, Hideaki Yamabe. After Hide returned to Japan, we remained in contact.

In November 1991 Hide alerted me that he was coming to Seattle for a visit. When he arrived, I took him to a favorite Mexican restaurant of mine where the margaritas were famous. It was a fun evening and at one point the owner of the restaurant brought over a huge sombrero that Hide wore. The stories were light as we shared what we had been doing. Then, Hide somehow switched topics and asked me, “Have you seen any patients with kidney disease who also have an infection with the hepatitis C virus?”

Hepatitis C was a virus that had just been discovered only a few months before. It had been known that some people could develop a condition known as hepatitis in which their liver became enlarge and inflamed. There were already several types of viruses that were known to cause liver disease, and two of the most common causes were hepatitis A and hepatitis B virus, but there was another unknown type of hepatitis virus that especially affected those who had

received blood transfusions or had taken intravenous drugs in their past. Unlike the other hepatitis viruses, that often caused substantial symptoms, this newly discovered virus often caused minimal symptoms when people would come down with it, and classic symptoms of hepatitis such as turning yellow (jaundice) was rare. Indeed, when blood tests were performed to evaluate how well the liver was functioning, the tests were often only minimally abnormal. However, the bad thing was that, over time, some of these patients would develop progressive damage to the liver that could lead to chronic liver failure (cirrhosis) and eventually death.

The great thing was that the first blood test for the virus had just become available. Specifically, the test could measure antibodies in the blood that had developed in response to the infection by the hepatitis C virus. Importantly, the antibodies were not effective at eliminating the virus, and so their detection meant that the individual had an active, ongoing infection that otherwise would have not been known.

Hide's question almost went right by me, as I was not really thinking about medicine, and furthermore, the test for hepatitis C was so new that I had not tested anyone for the virus in my clinic. Afterall, I worked in a kidney clinic, not a liver clinic.

"No, Hide, I have not seen anyone with kidney disease and hepatitis C infection. Why do you ask?"

"Well, because I have found two patients with a rare kidney disease, that is MPGN[4] , and both tested positive. I was wondering if there might be a relationship."

I told him that I would look for such cases, but soon we moved on to better things and discussing medical research was no longer on our agenda!

The next day I went to the University Hospital as I was starting a clinical rotation as the attending of the kidney service. I arrived at the inpatient ward for the kidney service a little early, and hence found myself waiting for the clinical fellow to arrive. As I sat, I noticed a pile of charts of the patients who had been discharged over the prior week. More out of boredom than curiosity, I opened the chart at the top of the pile, and to my surprise saw that the patient had a discharge diagnosis of MPGN. It was sort of remarkable as I probably saw only one or two patients with this disease a year.

[4] For those who want the official name, it is membranoproliferative glomerulonephritis, but it is called MPGN because even though doctors love complicated names, it is too long to write in the medical chart!

Since Hide had said that he had seen some subjects with MPGN and hepatitis C virus infection, I raced to the laboratory results section. The kidney function tests were abnormal as expected for a person having MPGN, but the tests for the liver were also abnormal, but these latter tests were so mildly elevated that most doctors would not consider them significant. The observation of mildly elevated liver function tests, however, could be consistent with hepatitis C infection, but the patient had not been tested. However, he had been tested for 'rheumatoid factor', which is normally a test for rheumatoid arthritis. However, this test is also often obtained in patients with kidney disease since some individuals with MPGN have high rheumatoid factor levels despite not having arthritis. Indeed, his level of rheumatoid factor was very high, and was consistent with his kidney biopsy report that showed he had MPGN.

I became interested in whether he might have hepatitis C infection. The laboratory could test for this it if there was blood available, but he had been discharged from the hospital a few days earlier. However, it struck me that the lab might still have some of his blood, especially given that he had tested positive for rheumatoid factor, as I was aware that the laboratory would often hold onto serum samples that were dramatically positive for particular tests since they would use them in the future as positive controls. Sure enough, when I called the laboratory, they had the serum. I told them to hold onto it.

After rounds, I walked to the laboratory and picked up the blood specimen and took it to the microbiology laboratory where a young virologist, David Gretch, was working. David was running the new laboratory test for hepatitis C, but was also developing much more sophisticated tests including testing for the virus itself. When I told him what Hide had shared with me, he became quite interested in whether the patient might have hepatitis C virus infection as well, and he offered to test the specimen with all of his special techniques. Within a couple of days, we had an answer. Not only was the patient positive for hepatitis C antibody, but he could demonstrate that the virus was present in the patient's blood!

I knew I had to reach the patient, as he had been sent home on steroids that would help block the inflammation but would have no effect on killing the virus. However, a drug called interferon had been recently used to treat the hepatitis C virus, and it some patients it had a remarkable benefit, although it could be associated with side-effects. I realized that if I could get him on treatment, I might be able to help him rid the virus, and perhaps might just improve the kidney disease as well.

I went back to the Medical Records Department and found his chart, and went to the page where his personal information was supposed to be. He lived in a remote town in Alaska, and there was no specific address and no phone number. Drat! But the chart did provide the name of his mother with her phone number. So I promptly gave her call.

"Unfortunately, he lives in a little apartment and does not have a phone, and he is often fishing for months at a time, so it is very hard to reach him. I am so sorry."

"But there must be some way you can reach him. Does he have any friends up there that I might be able to reach?"

"Not that I know of. But, come to think of it, he frequents a bar. If you could track down the bar, you might be able to reach him."

The task did not look simple, but I called the Information line for his Area Code, and to my delight was able to get the phone number for the only bar in the town. Realizing it was a long shot, I called the bar and reached one of the bartenders.

"Sure, I know him. He is out to sea right now, but next time he comes in here, I will tell him you called. Let me take your phone number."

I gave the bartender my number, but I was sure I would never hear from the patient again. Indeed, after several weeks passed, I pretty much quit thinking about the case.

Then one day, as I sat in my office, I received a phone call from a phone booth outside the bar in Alaska.

"Doc, I got your phone number from a friend, and I am so glad you reached out to me. I have been at sea for weeks, and I am miserable. The treatment (steroids) isn't working. I am all swollen, I can barely get my feet in my shoes. I have blotches all over my body. Doc, I am weak, I feel like crap."

"I understand. I might be able to help you. It turns out that we found you have a virus infection---a type of virus called hepatitis C. It is known to cause liver disease. Did anyone ever tell you had a liver problem, such as hepatitis?"

"No, not that I know of."

"Well, we need to check that out. But more importantly, I have a hunch that it may be causing your kidney disease. And the good news is that there is a treatment. But it would require you coming back to the University of Washington. "

Before I could finish my sentence, the man said, "Doc, I will fly down TOMORROW."

Amazing. He flew down the next day, and I immediately saw him in the clinic. Frankly, he did look miserable, as his legs were filled with water and he had dark purple blotches over his arms and legs. Further tests showed he also had chronic liver disease. I realized he needed to be treated with the drug, interferon. However, since I did not have personal experience giving interferon, I contacted Dr Richard Willson at Harborview Medical Center in Seattle, who had more experience. Together, we started to treat him with daily injections. To our delight, he started improving within a month, and his kidney disease stabilized and the swelling and rash went away. He did have a side effect in which he would sometimes call me a saint, although sometimes he would also call me the devil, but overall he continued to improve weekly.

We had a conference several months later in which we could present our work to other kidney and liver physicians, and so I told the story about my patient and asked the doctors in the audience if they had seen similar cases. Within a month I had 3 more patients referred to me. I also contacted my friend Hide, who was now back in Japan, and he said he now had 3 patients.

We combined our cases and, along with David Gretch and Richard Willson, submitted the paper to the *New England Journal of Medicine*, which is one of the top medical journals in the world. The paper was published and brought further attention to our work, and within a year I had over 40 patients that I saw in clinic with this disease. Over the next years, thousands of subjects with hepatitis C infection associated with this type of kidney disease were treated throughout the world. While the use of interferon was largely effective, the problem was the disease would commonly relapse when the treatment was stopped. But in the last 10 years there have been newer medications developed, and today it is easy to cure a person of hepatitis C-associated kidney disease.

Observation is often the first step to a discovery. Importantly, you do not have to be a genius or expert, but being curious and passionate helps. In my case, I did not even make the original observation. Rather, it was made by my friend, Hide, as I simply was a passionate opportunist! So what can we surmise? As my mentor, William Couser told me when I started doing research in his laboratory, it is better to have a B+ mind and an A+ effort than an A+ mind and a B+ effort. At the time, I did not know which group he was categorizing me in. But today I know—it is the drive that counts, it is just the drive.

Chapter 2 Followed by a Question

"You see, but you do not observe. The distinction is clear."

Sherlock Holmes, in ***A Scandal in Bohemia*** by Sir Arthur Conan Doyle

It was Halloween night during my second year at the University of Wisconsin in Madison, and, perhaps not unexpectedly, my friend Trout and I decided to dress up as Sherlock Holmes and Dr Watson. Trout was an engineering student who was (and still is) ingenious and creative, but not always with successful consequences. For example, one night he decided to get back at his roommate in our dormitory for coming home very late every night. I watched Trout as he precariously balanced an egg on two pins over the door, and then tied a thread measured just at the right length so that when the door was opened to the right spot that one of the pins would be pulled out and the egg would land on his roommate's head. An engineering achievement, for sure, and when Jack came home that night it worked as planned, with the egg landing exactly on Jack's head, causing the egg to crack, then to his shoulder, where it cracked some more, and then broke on the desk next to the door, ruining Trout's term paper that had taken him hours to type. With such skill, I knew Trout was the perfect Dr Watson.

It was a spectacular autumn evening, and we wandered around campus and up State Street, where we visited a few bars (of note, the drinking age was then 18 years) and hamburger shops. All night we created little mysteries that we would pretend to solve, whether it was the 'Matchstick Murders" or the "Case of the Missing Bartender." But it was getting late, and so we headed back to our dormitory, climbing Bascom Hill with its amazing view of State Street with the Capitol in the distance. As we neared the top, we decided to climb up the famous statue of Lincoln so we could take a few minutes to enjoy the view. As we did so, we noted that someone had smashed some pumpkins on and around the statue, but it was a beautiful night and we did not let that bother us.

As we were sitting, Watson pointed at a police car that had its lights flashing and was driving up the road alongside Bascom Hill. "Look at that, Sherlock, the police are after someone."

Within just a few minutes, several more police cars started driving up the hill. I looked at Watson, "Someone must have done something really bad! We might have to investigate this!"

"Sherlock, look--- they are even bringing a paddywagon."

Sure enough, a police van drove up with its lights flashing. It looked like someone was going to be arrested. And it seemed like it was likely right around where we were, as all of the police cars stopped at the top of the hill. This was getting interesting. Perhaps Sherlock Holmes and Watson might be able to help catch these criminals.

"Look, Sherlock, there are a number of officers walking over towards us. Perhaps they need our help." But then we saw that they had their hands close to their belts, and they began to circle the statue.

The police had come for us!

"Boys, get down off that statue, immediately, and tell us your names."

So Watson and I quickly got off the statue. Although I knew they wanted our real names, I just could not resist. "My name is Sherlock Holmes, and this is my loyal friend Dr Watson."

The head police officer cracked a smile, "So we have Holmes and Watson, very good. Are you boys responsible for smashing the pumpkins on the statue?"

"No, sir, we are innocent, but we might be able to offer our help to identify the villains."

"Boys, I recognize this is Halloween, but you should know that it is illegal to cling to the statue."

"Cling?" I said in a puzzled tone.

"What I mean is climbing up on the statue."

"Sir, we were only on the statue to enjoy the view. And I repeat, we are not the ones who smashed the pumpkins."

"Very well. We will let you off this time. But first you have to climb back up and remove all of the broken pieces of pumpkin."

That of course we did, and despite our proposal, we were not asked to investigate the original perpetrators of the crime.

I tell this story only to emphasize that, even when I try to be Sherlock Holmes, I could see the many police cars, but not realize that they were coming after us, likely because I considered myself innocent. *I could see, but not observe*!

So why can two people see the same thing, but one gets an insight that leads to a discovery and the other does not? Of course, there are many reasons, but there is one special aspect that is common among discoverers. And that is that the observation gives an insight, true, but that it transforms into a question. Specifically, a question in which a possible answer is included. Classically a "*What if*…." type of question, such as "*What if* they think we are the criminals?"

In the medical world, we call this question a "hypothesis". Like Vogl's observation that then triggered the question, "what if this drug might function as a diuretic?" when he saw an unexpected increase in urine output following administration of the drug. Generating a question, especially if it is linked with a possible answer, is how a lot of discoveries are made.

Inventions often occur the same way. Often it involves working on a project, that then leads to an insight into how to solve some other problem. To help paint cars, for example, an individual named Richard Drew experimented to make a light adhesive that could be put on paper and attached to cars during production to help prevent that part of the car to be painted. However, Drew had the insight to generate a question—can I apply this approach to generate a masking tape or scotch tape for general use?

Artists also use this principle. Many will first learn classical art skills to replicate their favorite artist. But then comes the idea of "What if" I alter this or that to generate something that represents more of my own creative art skills? From these types of personal modifications, the artist can develop his own style. This is why Pablo Picasso argued "Art is theft" and writer Austin Kleon wrote a book "Steal Like an Artist", because the roots of an artist's creation often come from someone else's work. But if you think about it, it is rare for new ideas to just happen. They do not appear out of thin air. Most are triggered by an observation, and one that triggers you to do something.

One of the great things about changing an observation to a question is that it then becomes something you can try to answer. It also allows you to ask small questions or big ones, and often it is just as easy to ask a big question as a little one. And always ask the big questions if you have a choice.

Types of Discoveries

This gets to the next issue, which is that there are many types of discoveries. Discoveries can include exploration (such as of the sea or space), cracking mysteries in our past, identifying fundamental theories in mathematics and physics, or identifying the cause of the disease. Heck, I get excited when I discover a beer in the back of my refrigerator. But, for the purpose of this book, we will focus on scientific discoveries, and especially those involving medicine. Nevertheless, as I mentioned, the stories I will share are relevant to anyone with an interest in creativity, art and inventions.

Discoveries can range from small to big, and from obvious to unexpected. Most discoveries, at least in medicine, tend to result from small, *incremental innovation*. Usually this involves a physician or scientist who joins a laboratory that is long-established and is working on a very narrow topic. Often much is known about the topic, and observations that are made lead to questions that are subsequently tested by rigorous experiments known as the scientific method. Often hundreds of experiments are done, generating volumes of data that can refine a story, or can connect a few of the missing dots in a picture. While any publication from such research may appear minor and of little impact, the net effect of multiple incremental studies on this narrow topic can be significant. Collectively, in fact, the multitude of studies can provide overwhelming evidence that can move the field. Indeed, the power of incremental innovation lies in the number, which can 'move the needle' better than almost any other approach. In some ways, it is sort of like "strategic" chess in which the goal is to continuously make small moves that subtly strengthen your position until your situation is overwhelming. Incremental innovation is how much of the science in the world is established.

Discovery can also be dramatically accelerated by *technological innovation* which often manifests as a type of invention. When Antonie van Leeuwenhoek used his novel spherical lens to make a microscope, he enjoyed shocking the ladies by showing them the horrid swimming bacteria that lived in their mouths. However, the impact of finding these "little eels' was the first visualization of germs, that being living microorganisms that had the capacity to pass disease. Likewise, when Galileo gazed at the skies with the recently-invented telescope, his discovery of the moons of Jupiter provided evidence for the first time that, at least for these moons, the earth was not the center of the universe.

Some of the greatest technological breakthroughs in medicine have been in the world of molecular biology. Today we can identify and characterize the genes in our body (using the polymerase chain reaction or PCR) as well as how to modify and repair them (using the CRISPR/Cas9 gene scissors). This led to a Nobel prize to Kary Mullis in 1993 (for invention of the PCR) and to Emmanuele Charpentier and Jennifer Doudna in 2020 (for the invention of the CRISPR/Cas9 gene editing method). We have not only cracked the human genome but these new breakthroughs provide an opportunity to cure many genetic diseases.

So technological innovation is a major tool for new discoveries. Of note, we have screwed up as well. For example, the Nobel prize was given to António Egaz Monis in 1949 for introducing the frontal lobotomy as a treatment for schizophrenia. Over 5000 individuals got this treatment before it became clear it did more harm than good. As one of my friends told me, "I would rather have a bottle in front of me than a frontal lobotomy." Here, here, I agree. This procedure should never ever be done.

While incremental discoveries are common and slowly move the needle, every now and then major discoveries are made that can have significant impact. In chess this would be considered tactical play in which a few dazzling moves can lead to victory. Here there are really two major types—***intuitive*** and ***disruptive***. An *intuitive innovation* is a discovery that fits within current thinking but represents a substantial jump from current science. For example, the introduction of antibiotics was an intuitive innovation as it was strongly believed that there might be a chemical that could act as a "magic bullet" to kill bacteria based on studies with vaccines and antisera. The discovery of the first effective antibiotics therefore represented a major advance in medicine. Discoveries of this type are heavily celebrated and quickly impact the field. This can result in the individual receiving the Nobel Prize within a very short period of time.

The other type of discovery is the most exciting of all, for which I give the term, *disruptive innovation*. These are innovations that challenge current thinking and suggest that what our teachers and textbooks have been teaching us is wrong. Disruptive innovations occur when an experiment generates results that clash with what has been considered gospel. They are often the most exciting, but also the most difficult for scientists and the public to accept. As the philosopher Thomas Kuhn wrote, a disruptive innovation is one in which "one conceptual world view is replaced by another."

Disruptive discoveries are often viewed with skepticism and are attacked vigorously. Later, however, they become the new dogma. Copernicus, for example, was challenged by the Church for his premise that the earth rotated around the sun and not the reverse. Darwin was also the target of much criticism for his theory of evolution from both religious men and scientists alike. The German philosopher Arthur Schopenhauer (1788-1860) aptly described a disruptive innovation as follows: "All new science goes through 3 phases. First it is viewed as ridiculous. Second it is vehemently denied. Third it is viewed as self-evident." Max Planck was perhaps more bitter the way he described it: "A new scientific truth does not triumph by convincing its opponents, but rather because its opponents die, and a new generation grows up that is familiar with it".

One way to view the different types of innovation is to think about Christmas trees. If you make a new ornament, you make the tree prettier, but it is simply an extension of what was already made, and so it represents an "incremental" change. If you ask yourself, why do I need a live tree, you may end up with a slightly more innovative (and technological) solution, that of creating an artificial Christmas tree with lights. A bit more innovative is to ask the question, why do we need lights at all, and engineer a tree that expresses a fluorescent protein in its leaves, so that it naturally lights up at night. Finally, one could ask whether it is necessary to have a tree at all, and create a hologram of a Christmas tree that could be put in your own living room. Imagine, one day we might be able to have holograms of Santa trying to fit his way down a chimney on our houses! Interestingly, in today's culture, these breakthroughs might all be viewed as a mixture of technological and intuitive innovations, as the basic premise of having a Christmas tree still exists. In that regard, if someone made the case that the Christmas tree was evil or dangerous, and that the tradition of having Christmas trees should be abolished, and that we should switch to worshiping rocks on Christmas, then that would be a disruptive innovation.

So, it may be helpful to just describe two actual discoveries, with one being an intuitive discovery and other being a disruptive discovery. Of note, both individuals received the Nobel prize for their important work.

The Discovery of Insulin

Diabetes mellitus, or diabetes for short, is Latin for the 'sweet disease', as it is a condition in which glucose (often referred to as blood sugar) soars in our blood to very high levels, and also

passes in excessive amounts into the urine. **“**The ants flock around the urine”, the great Indian physician Sushruta said about what happened to those who were afflicted with diabetes. The urine is “wonderfully sweet, as if imbued with honey or sugar”, wrote Thomas Willis, the Sedleian Professor of Philosophy at Oxford. Matthew Dobson, a physician from Liverpool, was even able to boil 4 pounds of diabetic urine, generating 4 ounces, 2 drams (teaspoons) and 2 scruples (like a pinch) of a whitish sugary cake that "smelled sweet, like brown sugar, and could not be distinguished from sugar, except that the sweetness left a slight coolness to the palate”.

Now I do not recommend tasting the urine of a diabetic patient, no matter what my father taught me. Furthermore, having diabetes is anything but sweet, for once diagnosed, the disease can be fulminant, especially in children. Typically, a child with diabetes presents with marked thirst and frequent urination, often with rapid weight loss. Many progress to a condition called ketoacidosis, in which acid builds up in the blood, causing rapid breathing and the peculiar smell of acetone on their breath. This is the most serious complication and can proceed to coma and death. There is also a milder form that typically affects older subjects who tend to be obese. But the greatest concern is when it affects a child for it can take his or her life in just days.

Thankfully, the disease was rare, and in 1890 studies reported that it only affected one in 50,000 individuals. But, beginning in the 1890s, it began to increase, and by 1920 the disease had become twenty times more frequent. This may still sound ridiculously low, but at that time it was a reason for great concern. Afterall, there was no effective treatment. Little did they know how diabetes would increase further over the last 100 years, affecting more than 10 percent of adults in America today.

Back then the goal was to find a treatment. In that regard, a Russian scientist named Oskar Minkowski had discovered that diabetes developed in a dog if its pancreas was removed. [One story suggests it was discovered when a lab assistant noted the dog was urinating a lot and that the urine was attracting flies]. This finding led Minkowski to propose that the pancreas might contain a substance whose role would be to lower blood glucose. Others suggested that a special type of cell that concentrated in tiny “islands” in the pancreatic tissue (called the Isles of Langerhans and not to be confused with the Shetland Islands off the coast of Scotland) might be the source for this glucose-lowering hormone. Yet there was no proof that this ‘isletin’ substance existed, and, moreover the injection of ground-up pancreatic tissue into animals tended to be toxic and ineffective at lowering blood sugar.

Enter Frederick Banting. Frederick had been raised in rural Canada. He was known in childhood as shy and somewhat of a loner, but he also was quite driven and would study for long hours. Despite that, he was considered average by his teachers, and his school principal remarked later that no one would have predicted Frederick to do what he did.

Early on Banting decided he wanted to be a doctor, and because of his hard work and study habits, he was accepted to the University of Toronto Medical School where he majored in surgery. When Canada entered World War I in 1914, Banting applied twice to join the Canadian Expeditionary Force but was rejected for poor eyesight, but after graduating from medical school in December 1916, he was accepted into the Canadian Medical Army Corps. He ended up in France where he worked as a medic and assisted the wounded in battle. Then, in the Battle of Cambria in northern France, he found himself under fire while positioned in a sunken road, and after being there an hour he rushed for safety but was injured when an exploding shell sent shrapnel into his right arm. Despite a significant wound, he continued to help other wounded soldiers for the next 16 hours. For his bravery, he was awarded the Canadian Military Cross.

On returning to Canada, he worked briefly in the Hospital for Sick Children in Toronto, but was unable to obtain a permanent position, so in July, 1920 he moved to London, Ontario where he set up a clinical practice as a surgeon with particular emphasis on orthopedics. It was difficult finding enough work, however, and in his first month he had only one patient and a net of four dollars for the visit. So he applied to teach in the University of Western Ontario which was a new medical school in London. While he had minimal training as a teacher, he argued that he would read ahead of the class to make sure he could teach effectively.

That fall he was teaching anatomy and physiology, and then a telling event happened. On October 31st, he began to prepare a talk on the pancreas and its potential relationship with diabetes, when he received a medical journal (The Journal of Surgery, Gynecology and Obstetrics) in the mail that had an article by a pathologist named Moses Barron. The article discussed a patient who on autopsy had a stone in his pancreas. The pancreas is mainly composed of cells that produce enzymes that travel down a duct (which is like a tube) to the intestine where they assist digestion. There are also some collections of different types of cells that are scattered throughout the pancreas and look like islands, and, as mentioned earlier, were thought to represent the cells that make the glucose-lowering hormone. Rarely, stone-like debris originating from the gallbladder could block the pancreatic duct, thereby preventing the enzymes from reaching the pancreas. When this

happened it could result in severe inflammation and a painful condition called pancreatitis, although rarely the pain is subtle. What was striking in the report by Barron was that, the chronically obstructed pancreatic duct in the patient was associated with a remarkable loss of the enzyme-containing tissues which had shrunk and shriveled, leaving only scarred tissues, while the island-types of cells appeared to be preserved.

That Halloween night Banting went to bed but could not sleep, and tossed and turned while he continued to think about this article, and how it might relate to diabetes. He recalled that people had thought that the islets were the source of this mysterious glucose-lowering hormone, but when people tried to inject pancreatic extracts into diabetic animals, there was no benefit. Finally, around 2 am Banting jumped out of bed. Perhaps the reason no one had found the hormone was because it was being "chewed up" by the enzymes from the pancreas during the process of preparing the pancreatic extracts. However, *what if* he tied off the pancreatic duct of a dog and allowed its enzyme tissues to dry up such that all that was left were the islets? Then it might be possible to extract the "isletin" or "insulin" without losing its potency during the isolation process. Perhaps then it could be given to people with diabetes.

The next day he met with FR Miller, a physiologist in the University in London Ontario to see if he might allow him to conduct experiments, but Miller referred Banting to Dr John Macleod at the University of Toronto, who was the Head of the Department of Pathology and a world expert on diabetes.

The meeting between Banting and Macleod occurred in November 1920 and did not go well. Macleod was a Professor with years of research in the field of diabetes. Banting was a 29-year old physician in private practice with no research background and minimal knowledge about what research was being done in the field of diabetes. When Banting presented his idea, Macleod was skeptical and wanted to know why Banting thought he could be better at finding insulin when others with much more experience and knowledge in the field had failed. Despite Macleod being a nonbeliever, Banting persisted in his desire, meeting with him at least two more times. Eventually Macleod ended up inviting him to work in his laboratory during the summer but again warned that he would likely have negative results. Nevertheless, Macleod offered to pay for the dogs and to hire a medical student for him.

There were two medical students interested in working with Banting, and they had to flip a coin to see who would get the position. The winner was Charles Best, a young 20-year old who

was just finishing undergraduate school at the University of Toronto after having served in the war. He supported himself through school by playing professional baseball. His first day in the laboratory was the day after he completed his undergraduate exams.

Best and Banting began their studies on May 17th, 1921. Banting performed the surgery of tying off the pancreatic duct of the dog, and Best was in charge of isolating the pancreatic extract and measuring the blood and urine glucose (sugar) following its injection into diabetic dogs. First, however, then they had to wait until the pancreas scarred down to only leave the islets. One month after beginning the experiments, Malecod left for Scotland to visit with his family for the summer, leaving Banting and Best on their own. A month later, on July 30th, Banting and Best prepared a pancreatic extract from a dog with chronic pancreatic obstruction, and injected the extract into another dog that had had its pancreas removed and was now diabetic. The blood sugar fell approximately 40 percent. When Macleod returned from Scotland in September, Banting presented his exciting results, but Macleod remained skeptical and asked Banting to repeat his studies. Banting became angry that Macleod did not believe in his work, and threatened to move to another University, resulting in Macleod persuading him to stay with additional support for the laboratory including a modest salary of 150 dollars/month.

In the meanwhile, Banting had learned that it was not necessary to do the surgery, but that they could get success from using cow pancreases, and with the help of a chemist, James Collip, as well as Macleod, they found that they could concentrate the substance in an alcohol-based extract. By January 2022, Collip had identified a purified substance that they called insulin. Meanwhile, Banting and Best were able to induce a dramatic fall in blood sugar in a diabetic dog with the alcohol-based extract.

The timing was right. Banting had learned that a 14-year old boy, Leonard Thompson, had been admitted with diabetes with ketoacidosis. On the night of January 11th, Banting and Best went to the hospital, and watched as a medical resident injected the extract into the child. To their delight the blood sugar fell significantly. After a week, more purified preparations were made with even more efficacy. A treatment had been found.

Within days the production of insulin began, following Collip's suggestions. At first production was slow, but soon various companies became involved, especially Eli Lilly. By late 1922 treatments were becoming available, and remarkable cases of survival were recorded.

The very next year (1923) the Nobel Prize in Medicine was awarded to Frederick Banting and John Macleod. Banting was upset that Best was not included and gave him half of his share of the prize. Likewise, Macleod provided half of the money awarded to him to John Collip.

Banting was not trained in research, was not an expert on diabetes, and, at least while in school, did not stand out for being exceptionally smarter than others. In fact, he was an orthopedic surgeon in private practice[5]. Who would think that this person would make one of the most important discoveries in medicine? But what drove him was his surgeon-like mentality coupled with compulsion and persistence to identify a treatment for this important disease. Part of this drive related to both having friends and family suffering from this disease. For Banting, it was one of his friends, who became diabetic during the World War and for whom Banting was one of the first to treat, beginning in February of 1922. For Best, it was his aunt, who had died only a few years before from diabetic coma.

As Banting himself wrote, "Ask the 'why' of every statement and think out your own answer. If through your thoughtful work you get a worth-while idea, it will get you. The force of conviction will compel you to forsake all and seek the relief of your mind in research work…. I am a firm believer that you can do and be anything that you wish in this world, if you are prepared to make the sacrifices, think and work hard enough and long enough".

The discovery by Banting was an **intuitive innovation**, as the scientific field believed that insulin existed, it is just that no one had found it. That is why the time from discovery to practice was short, and why the Nobel prize was given just one year after the discovery. However, the next story is totally different—a discovery few people believed, many denied, and most thought was crazy.

Could Peptic Ulcer Disease be Caused by Bacteria?

By the early 1980s there had been a major advance in the management of peptic ulcer disease. Previously, diseases such as gastritis, gastric ulcers and duodenal ulcers had been very

[5] One of the great rules my father taught me is to never make fun of a person's name, mental or physical handicaps, faith or color. Basically, anything that an individual is born with or which he or she cannot control. But occupations were fair game! And in medical school, the orthopedic surgeon was one of our favorite targets! Indeed, the classic joke was that if you want to hide something from a surgeon, put it in the patient's chart, if you want to hide something from an internist, put it under a bandage, and if you want to hide something from an orthopedic surgeon, put it in a medical textbook. But let stereotypes be damned! Here an orthopedic surgeon in private practice made a discovery that has subsequently saved hundreds of thousands of lives. Hip hip hooray!

hard to treat. People would take antacids and Pepto Bismol (bismuth subsalicylate), but often it would not be enough and they would have to undergo surgery that often could lead to lifelong complications. But by the late 1970s, a new drug had been introduced, known as cimetidine. This drug could significantly reduce the acid production in the stomach, and it could control the pain in many and often lead to some healing of gastric or duodenal ulcers. Nevertheless, it was not perfect as relapse was common if the drugs were stopped.

One of the problems was that the cause of peptic ulcer disease was not known. It was largely thought to be due to excessive acid production by the stomach, driven by excessive psychological or emotional stress, or spicy foods, alcohol, or to the use of medications such as aspirin or indomethacin. And while these are all risk factors for disease, no one considered the possibility that the underlying problem might be due to an infectious disease!

The story begins in 1981 when a young medical resident named Barry Marshall was working at the Royal Perth Hospital in western Australia. As part of the residency training, Marshall had to do a small research project each year. In the prior year he had done some research in marathon runners who had developed heat stroke under the hot Australian sun, and he thought he might continue research on that topic. However, he had just started a 6-month rotation in gastroenterology when he learned that a pathologist named Robin Warren had a very interesting project.

Warren worked in the basement of the hospital where the pathology specimens would come for analysis. An interesting man who drank strong black coffee and smoked small cigars (cigarillos) at work, he met with Barry and told him of a very unusual observation he had made. Specifically, when he would look at the biopsy tissues from patients with ulcers, he would do the usual checking to make sure there was no cancer and to describe the severity of the gastritis and ulcer. However, he had noted that often he might see bacteria in the ulcer or around it. This could be best seen when he used a silver-based stain that would stain the bacteria black and make them visible. Furthermore, the bacteria all looked similar, being small and curved. It struck Warren as something odd and unexpected since the stomach contains a lot of acid and, as such, bacteria are not thought to be there.

The question Warren posed to Barry was whether he might review the medical charts of 50 or so of the patients who had biopsies showing these bacteria. Could their presence correlate

with any clinical finding? And if so, is it possible that the bacteria could have a role in symptoms and or disease?

Marshall was intrigued, especially since one of the patients on the list was a patient he had admitted with abdominal pain and for which no diagnosis had been made. Over the next few weeks he reviewed the charts of patients both who had and those who did not have the bacteria present in their biopsies. There seemed to be an association with peptic ulcer like symptoms.

Marshall decided to do a larger study, a prospective study of 100 subjects who would undergo upper endoscopy for abdominal symptoms. In addition, he would try to grow the bacteria by having some of the biopsy tissue cultured in the hospital microbiology laboratory. Marshall knew that there had been a recent discovery of a curved bacteria that could cause food-borne diarrhea. The bacteria, called *Campylobacter*, could only be grown under special culture conditions, in particular, requiring a low oxygen setting. So he asked the microbiology laboratory to start culturing the stomach and duodenal biopsies using this technique.

Despite this approach, biopsy after biopsy yielded nothing. That is, until the 37th case. That person's biopsy was cultured right before Easter in 1982. Because of the holiday weekend, the microbiology laboratory did not have enough personnel to check the cultures during that weekend, and the cultures were left in the incubator for 6 days rather than the usual 2 days. When the cultures were finally inspected, some bacteria were growing![6]

When the data of the 100 cases were assembled, there was a striking finding. While the bacteria were often present in patients suffering from gastritis (inflammation of the stomach), they were especially common in those with gastric and duodenal ulcers. In fact, out of the 13 subjects with duodenal ulcers, all of them had the ulcers teeming with this mysterious bacteria.[7]

Over the next year, Barry continued to study the bacteria. He also developed a blood test and also began doing studies in which he would give antibiotics or bismuth to try to kill the bacteria to see if it improved symptoms. The evidence was mounting. The bacteria might be infecting the stomach and duodenum—could they be the cause of the gastritis and ulcers?

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[6] This story is sort of a repeat in the world of medicine. Sir Alexander Fleming discovered penicillin the same way. Fleming was growing bacteria in different culture plates, and after one long Easter weekend he returned to find some bacterial cultures that had been kept over the weekend. It was then that he discovered a mold (*Penicillium*) that was growing on a plate and suppressing the growth of the bacteria. This led to the discovery of penicillin. You may agree with me that it can be a surprise as to what can be resurrected over Easter weekend.

[7] These were later given the name *Helicobacter pylori*.

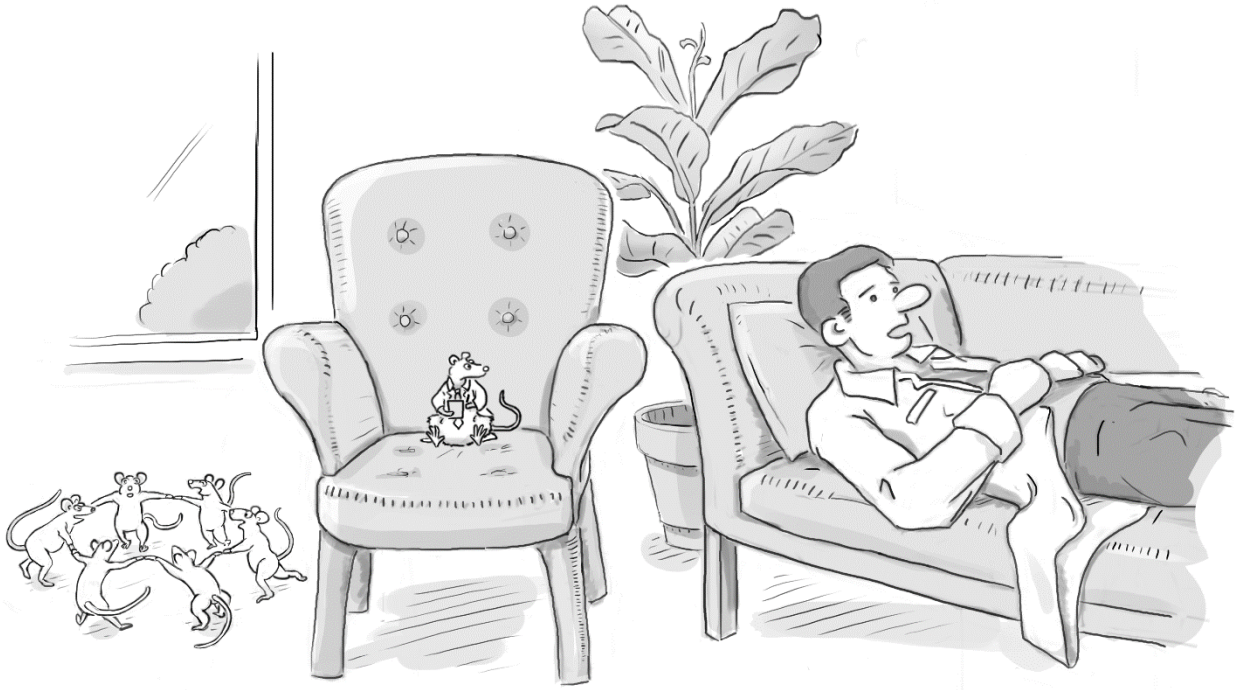
Marshall began trying different antibiotic combinations to see if he could rid the bacteria. Finally, he developed a specific combination of an antibiotic called metronidazole with bismuth and found that this combination eliminated the bacteria consecutively in four patients with an improvement in their symptoms.

The pushback, however, was high. Many people doubted him. Most experts continued to believe that ulcers were related to stress and diet. As Marshall wrote, *"I realized then that the medical understanding of ulcer disease was akin to a religion. No amount of logical reasoning could budge what people knew in their hearts to be true. Ulcers were caused by stress, bad diet, smoking, alcohol and susceptible genes. A bacterial cause was preposterous."*

As he became desperate, he began thinking about a bold experiment, one that might help prove that the bacteria were the cause of peptic ulcer disease. An experiment that would satisfy the skeptics. What if he were to ingest the bacteria and see if he developed gastritis? Indeed, he had maintained bacterial cultures from a patient he had subsequently cured, so he could treat himself the same way if he did develop gastritis or ulcers.

But there was a problem. He realized he should get permission from the Human Ethics Board, but what if they rejected his request? And he should also tell Adrienne, his wife, who was already stressed with whiplash and cracked ribs from a recent car accident and with the stress of raising 4 small children. Yet if he did not do this, he would not know, and what if he was wrong and what if he was right? And what happens when you have a passionate, impulsive individual who is dying to know the truth? Marshall decided to follow the "don't ask, don't tell" strategy and persuaded himself that his wife would recognize how important it was for him to do this key experiment. As Marshall wrote, "I had to be my own guinea pig….. .It was now or never."

He was able to persuade one of the gastroenterologists (Ian Hoslip) to endoscope him and to take tissues samples taken from his stomach to get his "baseline" status, and then later that day he went to the microbiology laboratory. There he persuaded Nick Noakes, one of the microbiologists, to scrape the bacterial cultures off the petri plate and to mix it with culture broth in a beaker to make a cloudy, brown-colored broth. Marshall then 'downed the drink' in one determined moment, a beaker of culture broth containing a rich culture of the bacteria. When he returned home that night he told his wife what he had done, much to her concern. But thankfully, she accepted this as she knew how much the world was challenging his findings.



I have been struggling with my identity, but I think I want to be a guinea pig.

Initially there were no symptoms. However, beginning around the 5th day he began developing fatigue, nausea, and shortly thereafter began to vomit in the early mornings. He developed severe bad breath, and had some abdominal pain. On the tenth day following the ingestion of the bacteria, he was endoscoped, and when the biopsy report came back it showed he had developed gastritis and that the inflamed stomach surface was coated with many of the curved bacteria. Interestingly, following the biopsy the nausea and vomiting subsided, and he underwent a third endoscopy on day 14 and the gastritis and bacterial infection had resolved spontaneously.

Nevertheless, Marshall had his proof that the bacterial infection could cause gastritis. The skeptics had been addressed. Later, as his work was confirmed by others, the impact of his work on peptic ulcer disease became clear, and in 2005 (23 years after the discovery), he and Robin Warren received the Nobel prize.

Both Banting and Marshall shared similar traits, but what a difference in the academic and public response! Banting made a discovery of what everyone believed but no one could find; while Marshall found something no one knew and no one believed. Both, however, followed the rule of changing an observation to a question. But what about the role of luck? Isn't this the biggest factor in discovery?

Chapter 3 Coupled with a Little Serendipity

"Name the greatest of all inventors. Accident." Mark Twain

"Luck be a lady, tonight". Perhaps you remember this great song from the musical, *Guys and Dolls*. One of the leads, a character named Sky Masterson, sings the song wishing that "Lady Luck" will not let him down that night, and will help him win a gambling bet.

Luck certainly seems to be important in gambling. I was also *lucky* to track down the Alaskan fisherman and connect his kidney disease with the hepatitis virus. I was fortunate that Hide shared with me his observation that a specific kidney disease might be due to a virus (hepatitis C). I was lucky to open the chart of a discharged patient and see that he had the rare disease. I was lucky to find a blood sample in the laboratory even though he had been discharged. I was lucky to find my microbiologist friend who tested the blood sample and showed it was positive for the virus. I was also lucky to track the patient down despite him being fishing out at sea and to be without a phone, and I was lucky to persuade him to go through treatment. To me, it seems obvious. 'Lady luck' helped me find the cause of his disease. I was in the right place at the right time.

What was especially cool was that I am definitely no Sherlock Holmes. At the time I was a junior professor and certainly not an expert. When expertise, genius, and special insight are taken away, the only remaining qualities I can hold onto appear to be luck and curiosity!

Serendipity! So many people have recognized how uncanny good luck occurring just at the right time can have a major role in discovery. It has even been argued that many discoveries occur not just by accident, but also can result from accident. One such discovery was made by a young cardiologist named Mason Sones who was working at the Cleveland Clinic.

The accident occurred on October 30th, 1958, in a laboratory in the basement of the Cleveland Clinic. A 39-year old cardiologist by the name of Mason Sones was performing a new technique in which he would inject a dye (known as contrast dye) through a catheter into the heart, and then perform X-rays that could image the dye as it travelled through the heart that could be used to visualize how well the heart was functioning. In this case, the patient was a 26-year old man who had rheumatic fever as a kid and now had developed rheumatic heart disease, a condition in which the valves in the heart can become diseased thereby affecting cardiac function.

Sones was known as a maverick who would smoke while in the operating room by using a forceps to hold his cigarette, and he was considered both "a genius" and a "pain in the ass"

depending on who you talked to. However, at that time, he was perched under the operating table where he was using the X-ray machine to take pictures. Assisting him was his resident, Royston Lewis, who had threaded a catheter into an artery in the leg and had advanced it so that it was now entering the heart. After Sones thought the catheter was in the ideal place, he told Lewis to inject the X-ray dye. To their horror, the dye did not go inside the heart chambers as it was supposed to, but rather went into one of the coronary arteries, the blood vessels that provide blood and oxygen to the heart muscle.

There was a general agreement in the literature that this could be very dangerous since the dye might interfere with the ability of the blood to deliver oxygen to the heart muscle. Sure enough, the young man's heart stopped, requiring Sones to jump out from under the table and give medicines to get the heart going again. He also told the patient to cough as hard as he could as this could increase the internal pressures in the chest and could help expel the dye from the coronary arteries. The patient ended up surviving the procedure.

Sones, however, realized that the ability to see the anatomy of the coronary arteries could be of great significance, as at that time there was a dramatic rise in heart disease due to plaques forming in the coronary arteries (coronary artery disease[8]). These cholesterol-rich plaques could cause blockage and heart attacks, and Sones knew that if it was possible to know where the lesions were, that it might be possible to one day operate on these patients and bypass these areas of obstruction by grafting blood vessels around it.

Most cardiologists would not have tried to repeat this procedure given how dangerous it could be, but Sones felt that that there could be great benefit from knowing where the lesions were in the coronary arteries. So, he started experimenting by using dyes that were less toxic, and also by giving smaller amounts of dye. Over the next few years, he performed close to 2000 angiograms. He even catheterized his mother when she complained of chest pain! Then, in 1967, one of his friends, Dr Rene Favolaro, used the information from a coronary angiogram to perform the first coronary artery bypass graft. Not long after, the procedure became the standard treatment for severe coronary artery disease.

[8] Coronary artery disease is the number one cause of death. However, for a long-time rheumatic heart disease was more common. However, coronary artery disease started to rise dramatically in the twentieth century, and was considered an epidemic by the 1960s.

While this story is sort of wild, there is another story about accidental discoveries that is also worth talking about, if only because it is an accident that continuously gets repeated. This relates to the discovery of artificial sugars, in which many were discovered because someone accidentally tasted it in a laboratory. The first discoverer was Constantin Fahlberg, who back in 1879 forgot to wash his hands and tasted a coal tar derivative that later was marketed as saccharin. Forty years later, a University of Illinois student discovered cyclamate when he was working on new drugs and accidentally tasted it while smoking a cigarette during a break. In the 1960s another scientist, James Schlatter, who was working for GD Searle and company, accidentally tasted a drug they were working on that later became aspartame, that is one of the major artificial sugars used in diet soft drinks. And in the1970s, a researcher by the name of Shashikant Phadnis was asked to "test" a sugar that had been chemically chlorinated and misunderstood the question to mean "taste", and so the discovery of sucralose was made. I think you get the idea—the discovery of many of the artificial sugars began as accidents that could have had bad outcomes, but instead led to a 'sweet' surprise (forgive me!).

Okay, I hope this helps dispel the concept that intelligence is a key criteria for discovery. Indeed, one might consider putting in an advertisement as follows:

Looking to Hire People Good at Discovery

No Expertise or Knowledge Required

Individuals who are Inexperienced, Sloppy and Accident-Prone are Desired

Especially if They are Curious, Passionate, and Willing to do Crazy Things

While this might be accurate based on the craziness of the last story, there is something about this that doesn't seem quite right. And so, we might do a little trick, and investigate what serendipity is *supposed* to mean. As it turns out, serendipity means a bit more than just being lucky.

Serendipity is a word coined by the writer, Horace Walpole, in honor of the adventures of Three Princes from Serendip (a country that today is called Sri Lanka). According to legend, the princes had been given the best education, and were known for being exceptionally bright, and also for having the ability to bring great fortune and luck to whomever they meet. One legend, which has been recently recounted[9], is that their father, the King, asked them to venture out from

[9] The Three Princes of Serendip, new Tellings of Old Tales for Everyone by R. Al-Galidi, Candlewick Press, 2017.

the kingdom to gain experience in the world. The three princes decided that the best way to learn about the world would be if they dressed as ordinary townspeople. So dressed as traders, they headed by caravan across India to distant Persia. They were close to the Persian kingdom when they met a sad and forlorn individual who had lost his camel.

"Have you seen my camel?" the man cried out.

One of the princes said to the man, "Did the camel have one eye?"

The man stared back in surprise, "Why yes, he did!"

The second prince then said, "And does he have a limp?"

The man nodded. "Yes, he did."

The third prince then said, "And is he missing a tooth?"

"Yes, yes, that is also true!" The man showed visible excitement.

The first prince continued, "And was the camel carrying butter and honey, with the butter hanging in a bag on its right side, and with honey on its left?

"That is my camel! You have seen him."

The first prince quickly responded. "No, we have not seen your camel." The other princes nodded in agreement.

"That is impossible. No one would know so much about my camel without seeing him."

Just then he saw some Persian Guards that were within earshot. "Guards, these men have stolen my camel. Make them give me my camel back."

The Guards arrested the three princes and took him to the head officer along with the owner of the lost camel.

"Officer, these men told me that they have not seen my camel, but they knew it was blind, had a missing tooth, that it limped, and that it was carrying both butter and honey. They are guilty, sir, and they need to be punished."

The officer, however, realized the importance of asking the princes for what they had to say. "Can you explain how you knew that this man's camel was one-eyed and lame?"

The first prince then spoke. "Yes, sir. When we were walking, we could see that the grass had been grazed only on the right side of the road, which suggested to us that the camel might be one-eyed so it could only see the grass on that side of the road. We also noted that there were tufts of grass sticking out at regular intervals that were consistent with how the grass would look if the camel was missing a tooth. We could see the footprints of the camel, and they were not regular but

rather were consistent with a weak left hind-leg suggesting that the camel had a limp. We also noted there were a lot of flies on the left side, and they tend to love butter, while we saw many ants on the right side, and they are known to especially like honey. This suggested that the camel was carrying butter in its left saddle bag and honey on the right, and that some of the butter and honey was spilling from the bags as the camel walked."

The camel owner gave quite an amazed look. "So, do you have an idea of where my camel may have gone?"

The second prince said, "Well, yes. It clearly was walking south on this road, and based on the fact there are still lots of ants and flies, the camel can only be an hour or two from here."

The camel owner thanked them and headed down the road, where he found the camel only a few miles away. He brought the camel back, and then thanked the princes, giving them some of the honey for their help. "It was my great fortune to meet you."

And the princes continued on their journey, bringing great fortune and luck wherever they went.

I do not know about you, but this does not sound like an example of pure luck, or as Webster's dictionary defines serendipity, "the finding of interesting or valuable things by chance." These princes weren't just bumbling along and happened to make a discovery, they were detectives that Sherlock Holmes would have admired. They were observant unlike I could ever be. I can be so much "in my own world" that, if a tornado took out my home, I would not have any clue until I could not find the door to the house. But these guys could tell if a camel was missing a tooth just by looking at clumps of grass. Of course, perhaps the story has been embellished just a little bit!

While it is a nice story, it is also depressing as it suggests that maybe I am wrong, and that maybe we do need to be geniuses to make discoveries. Clearly observation was more important for the discovery process in this latter story than I had originally suggested.

Consistent with this idea, I remember hearing about a brilliant physician who was presented a case of a 30-year-old man who was brought in coma to Harborview Medical Center in Seattle, where I had trained. Apparently, the man suddenly collapsed and was completely unresponsive when the medics arrived. The reason for why this happened was unknown. He was brought to the Emergency Room to be stabilized when the attending walked over and immediately noted that his feet, which were extending out from the sheets, had peculiar lumps on the Achilles heel. The physician recognized this as being lumps of fat (lipomas) on the Achilles tendon, a sign of a rare

disease known as Familial Hypercholesterolemia, in which individuals are born with very high cholesterol levels and can develop heart attacks at an early age. Testing confirmed this. Mystery solved! The diagnosis of a heart attack due to a rare genetic disorder that resulted in high cholesterol levels was made by simply gazing at the feet. And best of all, I recall the patient did well.

There was also another mystery case that I heard about, that, of all things, was solved at the Hammersmith Hospital, although I do not know if the person who cracked the case was the great Sir Keith Peters. The patient was a woman from India (there are a lot of south Asians living in London) who was admitted with swelling all over her body, in this case from a disease of the kidneys in which the urine was spilling large amounts of protein. When this happens the protein in the blood drops to very low levels, and this results in water seeping out of the blood into the tissues, causing the massive swelling. When the case was presented to the Attending, all seemed standard, until at the end of the presentation, the physician asked the registrar (as you recall, the name for medical resident in England) if he could ask the patient what type of skin cream she used. The question seemed odd, but when the patient was asked, she confessed to using a cream to lighten her skin, and in those days (and even in some parts of the world today) these creams often contained mercury. Indeed, the patient underwent a biopsy of the kidney to help make the diagnosis, and mercury was found in the kidney tissue.

Well, we may all recall how chronic mercury poisoning can cause confusion and excitability (recall the "Mad Hatter" in Alice in Wonderland who was a crazy individual, as mercury was used in hat making in the 1800s), but mercury has also been linked with this type of kidney disease. Apparently, the attending physician was aware of this connection and knew that it was being commonly used by south Asian women to lighten their skin. Amazing.

I tried to be a sleuth after I met a toxicologist, Peter Breysse, who came to me because he had seen someone who had developed a similar kidney disease after moving into a new mobile home. New mobile homes often contain pressed wood products that contain formaldehyde and can release fumes for weeks after assembly. Formaldehyde fumes are irritants that can cause sore throat, scratchy eyes, cough and general discomfort. Peter believed formaldehyde vapors might be causing much more widespread problems, and he asked me if it might be the cause of the kidney disease. I was intrigued, and he told me about a few cases he had seen. One thing that bothered me a little was that he thought formaldehyde might be the cause of just about every disease, so I was

a little concerned he might be "overcalling" his association. Besides, a lot of people have mobile homes, so if someone has a rare disease and lives in a mobile home, it could just be coincidence. Nevertheless, when I called the patients, I found that one of the patients was a builder who had used formaldehyde-containing products during the construction of a home, and he was bothered by the fumes and then a few weeks later came down with the kidney disease. A few months later, the person who moved into that same home also complained of the fumes and then developed the same kidney disease. This seemed like more of a coincidence, as this particular disease is reported to occur in about 1 individual for every 100,000 people.

I thought Peter and I had found another cause of kidney disease, and we wrote the paper up, publishing it in the *Annals of Internal Medicine*, a top medical journal. I truly expected I would receive lots of referrals from physicians around the country who might be seeing patients with this same kidney disease who had similarly been exposed to formaldehyde, similar to what happened when we found an association of Hepatitis C virus with kidney disease. But this time, no calls came. I also made a point to ask about possible exposure to formaldehyde from every patient I saw with the disease. So did my friends who were kidney doctors. Nada, nothing, no luck, I never saw another case. Nor has anyone else. Where was Holmes when I needed him? So much for my days trying to be a sleuth!

But all of this goes back to the question, how important is knowledge in converting an observation to an insight and then a question? Surely, observation is often the key initial step, but do we have to be like Sherlock Holmes? So let us look at two more 'serendipitous' discoveries to try to tease out what is luck, what represents ingenious detective work, and what just reflects persistence!

The Case of Margaret Tracy

In 1943, a young girl named Margaret Tracy was injured in a car accident in New York City. There was a delay in bringing her to the emergency room at Columbia-Presbyterian hospital, and when she was examined, she was found to have a compound fracture of her leg that was already infected. Areas of the wound contained pus and the skin was red and warm, consistent with infection.

The medical resident cultured the wound and sent the cultures to the microbiology laboratory. Balbina Johnson, the bacteriologist stationed in the laboratory, assumed that the wound

was likely infected with the bacteria *Staphylococcus* (often called Staph for short). This is the common bacteria that causes skin infections and was treated with penicillin, which had just become available for treating patients in 1941.

What struck Balbina Johnson was that when she stained the culture swabs for bacteria, she could confirm that numerous Staph were present, but when she examined the culture plates the next morning, no Staph had grown. Instead, there was a different type of bacteria growing on the culture plates, known as *Bacillus*, a bacteria that is commonly viewed as a contaminant from soil. Balbina Johnson, then had an insight—perhaps the *Bacillus* was making something that was inhibiting the Staph from being able to grow. Rather than just letting the idea go, she started experimenting to see if the Bacillus was producing such a substance. From this work she identified a new antibiotic, which she named "Baci-Tracin" or bacitracin, which is an antibiotic still used in many antibiotic creams. The name was made to immortalize the patient Tracy, as well as the source of the antibiotic-producing bacteria (Bacillus). I like this story as my daughter's name is Tracy, and this was also the name of my mother (yes, this is not a coincidence).

There was certainly some luck to this discovery, but there was also an insight. Was it genius? Perhaps not, because Balbina had to know the story of Alexander Fleming who discovered penicillin through an almost identical way. Indeed, a mold had contaminated the culture plates where he was growing Staph, and he had discovered it was making a substance (penicillin) that was preventing the Staph from growing. In fact, Fleming got the Nobel Prize just two years after Tracy's visit to the Emergency Room for his discovery that dated back to the late 1920s. So perhaps we can say Balbina was somewhat lucky that the culture was contaminated but that her insight perhaps did not require the assistance of Sherlock. But there is something else that is apparent, which is that Balbina Johnson did not just let this observation go. Rather, she was persistent in testing her hypothesis that the *Bacillus* bacteria might be making something that could inhibit the growth of Staph. Eventually she found that substance that proved her suspicion and brought a new antibiotic to the world.[10]

[10] BA Johnson. Bacitracin: A new antibiotic produced by a member of the *B. subtilis* group. Science 1945

Robert, I have discovered life on Mars!

A Misfortune with Serendipitous Consequences

Just as the dropsy could cause massive swelling and shortness of breath that could lead to a hasty exit in life, another great scourge was jaundice, in which a subject would turn deep yellow-orange that even affected the "white of the eye". While many patients would recover, some would develop a chronic disease in which the belly would fill up with fluid (called ascites), with muscle wasting, confusion, and a risk for gastrointestinal bleeding.

Early on it was recognized that jaundice was a disease of the liver, and while it could be from alcohol or other causes, there was also an infectious form caused by a virus. One type of infectious hepatitis (the name for liver inflammation) was especially common among people living in close quarters in situations of poor hygiene. This hepatitis is caused by the hepatitis A virus, and it is common among soldiers at war, including in the Napoleonic Wars in Egypt, and in the Civil War. People tend to recover from hepatitis A viral infection with little long-term consequences.

However, in the 1880s a second type of viral hepatitis was discovered that was associated with much higher mortality during the initial infection, and also could progress to permanent liver failure. The discoverer was a German physician named Lürman who worked for a shipyard in Bremen, near the North Sea. In October 1883, a shipyard worker came to Lürman with jaundice, and while that, by itself, was not so unusual, over the next two months nearly 200 workers presented with similar symptoms, with some dying from their illness. Lürman would have likely attributed this to the usual type of infectious hepatitis, but he noted that only a few months before that the ship workers had all been given a vaccine for smallpox. Vaccines were relatively new, and in those days they often contained human blood. Suspicious it might be involved in the outbreak, Lürman reviewed the records and found that all 191 subjects who had developed jaundice had received the same specific "lot" of vaccine that had been shipped on a particular date. In contrast, there were no cases of jaundice among 500 workers that had received a different lot of the vaccine.

Lürman published a paper on this, but no one seemed to notice. That is, until 1942, when 50,000 US troops came down with hepatitis after receiving another vaccine (this one for yellow fever) that also contained human serum. Indeed, the Surgeon General banned yellow fever vaccines containing human serum in April, 1942[11]. The vaccine had been thought to be safe as it

[11] Yes, not all vaccines have been safe in the past. The controversies over the benefit versus risks of the COVID vaccine are understandable. While clearly the initial introduction of the COVID vaccine was life-saving, the pros and cons of the vaccine are less clear in recent months as the viral infection appears to be associated with milder outcomes.

was heated to 56 degrees Celsius, but the virus causing the disease could survive these temperatures. Subsequently this second hepatitis virus was called hepatitis B and was different from hepatitis A as it could be passed by blood products, such as by transfusions or by sharing needles among intravenous drug users. Yet the identification of the virus remained elusive.

Enter Baruch Blumberg, a physician working at the Fox Chase Cancer Center in Philadelphia in the early 1960s. Blumberg had developed a way to identify proteins in the blood that were relatively unique to that individual. Specifically, he knew that people who received multiple blood transfusions, such as individuals with hemophilia, might develop antibodies to proteins in a blood transfusion that they did not share. Indeed, he found that a patient with hemophilia from New York City had an antibody that reacted with a protein from the blood of an indigenous individual from Australia (the Tiwi people). He named the protein the "Australia" protein and began to look for it in other blood specimens. He found that it was exceptionally rare in healthy individuals from the United States (1 in 1000), but that it was higher in individuals with leukemia. This gave him the idea that it might be a marker for leukemia, and he published this in a major medical journal.

He also found that this protein was commonly present in individuals with Down's Syndrome, a condition also associated with an increased risk for leukemia. This led him to serially test subjects with Down's syndrome for the presence of the Australia protein. Finally came an individual, a Mr James Blair, who was initially negative for the Australia protein but then on repeat testing turned positive. Worried he might be developing leukemia, the patient was admitted to the Research Unit. However, instead of having leukemia, he was found to have developed acute hepatitis, as noted by elevated liver tests. Around the same time, Barbara Werner, a senior technician in the laboratory who had been working with the various blood samples, also developed hepatitis. Suspicious, she tested her own blood and discovered that she also had developed a positive blood test for this mysterious Australia protein.

Blumberg and Werner then realized that the protein was not a marker for leukemia, but rather might be the mysterious hepatitis B virus that no one could find. Of course, it was aided by the knowledge that hepatitis B could be passed by human blood. Over the next few years their observations were confirmed, and the blood test for the Australia protein was used to screen blood to reduce the risk for developing hepatitis B. For his discovery, Blumberg received the Nobel Prize. Werner went on to become a physician and expert on viral hepatitis. Later the hepatitis B vaccine

was developed. Today hepatitis B viral infection is continuing to decrease in prevalence in the United States due to the vaccine and improved antiviral treatments.

Luck does have a role in discovery, but it is 'prepared' luck. The more you know, the more likely you will be lucky. As Gary Player, the famous golfer said, "The more I practice, the luckier I get."

I understand why Sherlock Holmes is the greatest detective. His observational skills are uncanny, and when luck runs his way, he perceives its relevance well before the rest of us. He has a 'prepared mind'.

The truth is I can never be like Sherlock. Afterall, I have gone to work and then noticed that I am wearing two different shoes—one black and one brown- and this has been a repeated offense. One time I noticed this heinous error right before I gave a talk to some medical students, and so I tried to avoid the embarrassment this would cause by slipping the shoes off my feet right before I went to the podium so that I could give the talk only wearing socks. [By the way, I was doing things like this even as a teenager, so it cannot be attributed to dementia)!

But all is not lost. There is another attribute that many discoverers have, and it supersedes having a "prepared mind". It is embodied in the movie hero, Indiana Jones, the archeologist who was always optimistic, impulsive and bold, and could laugh at danger while at the same time saving the world and doing so at the last second. This is what I call the "open mind", the ability to free one-self from the confines we live in, to go outside our normal boundaries, and to take on any challenge, all the while being playful at heart. And it is the playfulness that counts, for it is what frees the mind and opens the doors.

Chapter 4 and Playfulness…

"Every child is an artist. The problem is how to remain an artist once we grow up". *Pablo Picasso*

There is an old rule about research that thankfully seems to have been forgotten. This is the rule that if a person decides to do research, that he or she needs to show the same dedication and drive as their mentor, and this means the same "work ethic". Thus, if your mentor shows up at 8 am, you should do the same, and, likewise, when the mentor heads home at night, that too is the time you should leave.

While the rule was meant to test your fortitude and dedication to work, it actually had an interesting consequence, as it can provide a private glimpse about your mentor. One such story was shared with me by Dr Emily Cobabe, a paleontologist turned geochemist who ended up getting her PhD on evolutionary biology with Dr Stephen Jay Gould, the famous Harvard naturalist whose passion was evident in his writing. One night while she was in the laboratory, she thought she heard voices coming from Dr Gould's office. Curious, she walked down the hall to his office where the door was creaked open enough that she could peek to see what was happening. Gould was all alone, ecstatic and laughing, as he played with snails in his terrarium.

Often we separate work from play, but when work is play, the magic happens. When work is fun, no one is looking at their watch waiting for the day to end. Play generates high energy that people want to be a part of. Play can break boundaries that opens the mind to new ideas. In some cases, the playful attitude is a great way to cope when things are dangerous or challenging—this is where Indiana Jones becomes the hero. In other cases, well, it is only play, and it works just as well.

One of the best known examples was Sir Alexander Fleming, the discoverer of penicillin. Fleming loved having fun, and outside of work he played many sports (such as golf and tennis), and a lot of games (including bridge and snooker). He loved games so much that he would sometimes change the rules to make the game more fun and challenging.

His playfulness carried over to his work. Fleming was a physician who had served as physician in the Royal Medical Corps during World War I where he spent a lot of time working in makeshift hospitals in the battlefield. During this time he recognized the importance of developing antibiotics that could be used to treat the infections that often complicated battle wounds. So when he returned from the war, he went back to St Mary's Hospital in Paddington to be a bacteriologist. Here he spent much of his time growing bacteria in glass culture (petri) dishes.

Fleming was not known for being tidy or neat, and his work area tended to be a mess. One reason is that he had a game of using some of the culture dishes to make art. Specifically, some of the bacteria when grown would be white, but others might be red, green or even yellow. By using the culture swab as a type of paint brush, he could design patterns that would initially be invisible, but as the bacteria grew would transform into colorful art, from Christmas trees to ballerinas. This would require culturing the plates for a longer time than necessary. Indeed, it was over a long Easter weekend when he found that the bacterial cultures were being overgrown by a mold (*Penicillium*) that he recognized that the mold must be releasing some substance that was killing the bacteria. Some could argue that the discovery of penicillin was one of the greatest discoveries of modern medicine. As Fleming wrote, "I play with microbes….It is very pleasant to break the rules."

When I was in Couser's laboratory, there was a creative scientist named Mathias Schulze, for whom research seemed to be largely play. He loved to run complicated assays in which he would use a plate with 96-wells that would give him mounds of data. However, when he would finish the experiment, he did not like to throw the plates out. Initially they would be scattered all over his work bench and desk, but as he ran more and more plates, it began necessary to stack them. Pretty soon there were two, and then three, and then four huge towers rising off his benchtop, almost reaching the ceiling. He seemed to get great joy standing up on a chair and stacking more and more plates, until one day someone (I believe it might have been concerns from the fire hazard and biosafety group) made him throw them out. It was a sad day for Matthias. I am not sure why I am sharing this story, for he did not go on to invent LEGOS®. But he did publish his research in some of the top medical journals (including the New England Journal of Medicine). Whether building skyscrapers in the laboratory helped him get new ideas, I am not so sure. Most importantly, he loved research, and research loved him.

When it comes to playfulness and discovery, however, there is probably no one who better fits this role than Robert "Bob" Cade, the discoverer of Gatorade, a forever friend who I greatly admired.

It was the summer of 2003, and I had just received an offer to be the Head of the Kidney Division at the University of Florida in Gainesville, a position that was without doubt one of the greatest honors in my life. The University of Florida Kidney Program was not just any division—it was the division that gave birth to Gatorade, the first sports drink. The drink was developed by Bob Cade and his assistants Dana Shires, Alex DeQuesada and Jim Free during the mid-1960s when Cade was running the Division. What was exciting to me was that I would not just be Head of the Division, but also I would carry the title, the J Robert Cade Professor, or simply the 'Gatorade Professor'. So we made the move to Gainesville, a beautiful wooded community in north central Florida with majestic oaks, maples and pine trees surrounded by swamps and rivers, that was the home of (you guessed it), 'The Gators!'

Back in 1986, when I was living in Seattle, I remember the newspaper, the Seattle Times, announcing that alligators had been sighted in Green Lake, which was only one block from my apartment. I actually looked for them, even though everyone thought it was a hoax. That is, until two two-and-a-half foot-long baby alligators were found on the lakeshore. Apparently, some prankster had taken their pet alligators to the lake! But here in Gainesville, the alligators weren't little tykes--- these guys could be big, very big. And they could be anywhere—including in Lake Alice which was right on campus. When the sign says 'Do not swim here. Potentially unsafe," they are not trying to say the algae is blooming and that it might cause some respiratory complaints. Hell no! What they are saying is that you might get eaten if you go for a quick dip. These gators are not to be messed with, which is likely why the University football team was named after them (the Florida Gators) and why the football stadium is affectionately called the "Swamp." And Gatorade was not just Kool-Aid®, it was a drink to rescue the athletes suffering from the Florida heat in the 'battlefield" of college football.

You can imagine my delight that first day at work when I found out that Bob Cade was still active in the Division, and was continuing to do research in a hut in the fields near the Agricultural School. He had apparently moved his laboratory there during a rough period of history when there was a lawsuit battling over whether Gatorade belonged to the University or to the Gatorade

Inventors. The University ended up winning a share, but Cade remained in this remote laboratory even after the wounds had largely healed.

I arranged to meet him, and he greeted me with open arms, along with his assistant, Kelly Campbell, an individual who had been his right-hand for years and years. Cade loved to talk, share adventures from his past, and always seemed to have a new idea. He had an overwhelming personality that was characterized by generosity and kindness, outside-of-the box thinking, spectacular storytelling, and a perpetual sense of humor. He loved to recite poetry. He also remained innovative as it related to his research. For example, he told me he thought that dialysis might be able to cure schizophrenia, and how he had been doing some studies along that line. He told me about his life and he shared with me stories of some of his many inventions. Over time we became dear friends. When he, himself, went on dialysis, I even became his physician. When I look back, it is clear to me that what distinguished him from others, and what fueled his creativity, was that he was not just open-minded, but playful.

The Birth of Gatorade

James Robert "Bob" Cade was born in San Antonio, Texas in 1927, Robert showed evidence early on being a unique individual. As a boy he fell in love with poetry, history, and violin, and he we known to cite everything from Shakespeare to Lord Tennyson. He also loved to be a prankster. For example, when he was in sixth grade, he caught a football and made a touchdown. He was so excited that for the kickoff he laid on his back and balanced (t'eed) the ball off his nose for the kicker, Herbert Rossman. "Herbert kicked the ball and it went all to the way to our opponents goal, by far the best kick of the year." He ended up in the Coach's office being warned of his foolishness.

School was generally too easy for Bob and as such he often had to find ways to keep his interest. For example, in 9th grade he decided it would be a fun challenge to see how close to failing he could get on the first three examinations, with the goal of just beating a score of 60 (the bare passing level). On the first exam he scored a 61, on the second a 64, and on the third exam he received a 68. He then scored a 100 on the final examination. However, his teacher, Martha Henderson, did not find this amusing and gave him a C overall with a note to his mother that "I

am sorry to say that there is no favorable change in Robert's conduct or attitude since report cards were sent home. The greatest trouble is lack of self-control, lack of application and lack of consideration for those students who do want to work."

Bob left high school before graduating (he failed to turn in an essay) to join the Navy where he ended up as a sailor on a destroyer, a submarine, and eventually the cruiser, the Rochester. Here he sailed the Mediterranean, visiting North Africa, the French Riviera and the Greek Islands. After three years, he left the Navy and took an entry examination to get into the University of Texas in Austin and was accepted despite not having a high school degree. Here he completed most of a normal 4-year class schedule in only two years, and tested and was accepted into medical school at the University of Southwestern in Dallas, but again entered medical school without ever completing his college degree. As he wrote, "In fact, the only diploma I had, signed by Mrs Crane, testified that I had satisfactorily completed five years of work at Highland Park Elementary School."

Following medical school, he spent a year as a research fellow working with a famous physiologist, Dr Robert Pitts. However, an opportunity arose to come to the University of Florida in Gainesville and help establish a program focusing on kidney disease. In 1961 he arrived, with the goal of teaching young medical students, performing some clinical research, and overseeing a new subspecialty in which dialysis and transplantation were still in their infancy.

It was around this time that Dr Cade bought his favorite car, a 1951 Studebaker he named Ol' Spot, for just 10 dollars. "I learned over the next 200 miles that Ol' Spot got 26 miles per gallon of gas, 40 miles per quart of oil, and 200 miles per radiator full of water. I also found that when a car was tailgating us, I could put a huge cloud of bluish-black smoke between us and the tailgater, who when the cloud cleared was far behind us. He frequently came flying by us a few minutes later shaking his fist and yelling at us, words I couldn't understand with the window up, but he never tailgated us again." So now you know how Ol' Spot got his name.

Gatorade, the First Sports Drink

It was in 1965 when Bob Cade and one of his young faculty, Dr Dana Shires, decided to go to Atlantic City, New Jersey, where every year there was a major meeting on clinical research that spanned all areas of internal medicine. Dana was a tall engaging man who was not only bright

but also enthusiastic and loved research. At that meeting there was to be a talk by Sidney Malawer who had been a medical resident at the University of Florida but had moved to the prestigious research laboratory of Dr Franz Ingelfinger at Harvard. Sidney's lecture was scheduled for the last session of the last day, and both Bob and Dana wanted to show their support by attending his talk, especially since they knew that almost no one would be there since it was the last session of the whole meeting. Indeed, other than Sidney and Dr Ingelfinger, there was only one other person in the room besides Bob and Dana.

Sidney's talk focused on how nutrients such as glucose and salt are absorbed in the intestine, and that day Sidney pointed out that the absorption of salt was markedly increased (up to 4-fold) if glucose was also present. Apparently, the transport of glucose and salt were coupled, so that salt water alone could not be absorbed very effectively. After the lecture they took Sidney out for lobster dinner, and ended up at a movie theater where they watched "Zorba the Greek" late into the night.

Dana and Bob returned to Gainesville where only a few days later the triggering event occurred that would change their future. Both Bob and Dana liked to take a morning break for coffee at the hospital where they worked, and often they would be visited by Sergeant Dewayne Douglas, a security guard in the hospital who was known to frequent the coffee shop. Dewayne has been a varsity football player for the University of Florida Gators and had even been picked by the Philadelphia Eagles until a knee injury ended his career. Dewayne ended up returning to Gainesville where he was a line coach for the B squad football team and a security guard during the weekdays.

That day Dewayne joined Bob and Dana, and after a sip of coffee, asked a burning question, "Why don't football players wee-wee during the football games?" (Please note, I am not sure he actually said wee-wee, but it is what Bob Cade always said, though, with a smile).

Bob and Dana were initially quiet, but Shires, who had played football, agreed that this was common. So they began asking questions and soon learned that during a football game the players could lose 16 to 18 pounds in a three hour period. This raised all kinds of questions, not only for how much fluid was being lost as sweat, but also for how the football players might be

handling the heat from the Florida sun, especially given the heavy football uniforms and gear that the players had to wear.

Realizing that this was an important and interesting topic, Cade and Shires met early the following week with Ray Graves, the head football coach. They explained that they would like to determine exactly the degree of water and salt loss that was occurring during the games, and that their intention would be to design a drink that could help correct these losses and allow the team to perform better in the heat. Graves replied that this was fine so long as they experimented with the freshman team. While Cade has asked that they be volunteers, later he learned that Cunningham, the head trainer for the freshman team, simply pointed to various of the players "You, you and you… go down to Dr Cade's lab. He wants to experiment on you."

Two freshman football players, George Dean and Jim Yarborough, were key to the initial studies. Both were given rubber gloves that extended past their elbows (used by veterinarians for delivering foals from the birth canal of a mare) so that they would collect the sweat during a game. Other sophisticated measurements were also taken, although rectal temperatures were refused (Cade asked them to consider this since mouth breathing can give falsely low temperatures but got a resounding rejection to his request). At the end of the analysis, the results were striking. During just a two-hour practice in the hot Florida sun, it was possible to lose about 8 quarts of fluid from sweating. Not only was their water loss, but the salt loss was also significant, and the blood glucose level also fell to levels that could affect thinking. Even blood pressure fell to dangerously low levels.

One of the key findings was that, despite the loss of salt, the loss of water was greater, such that the salt concentration in the blood was actually high. Thus, the use of salt tablets, which was commonly being given, would have been a mistake. These individuals needed water, glucose, and some salt to replace the losses. And then there was the insight, the one that they had learned from the meeting in Atlantic City---giving glucose would not only help keep blood glucose levels in the normal range, but it would also help the absorption of salt.

That night, Bob and Dana, along with a medical resident (Alex DeQuesada), and a medical student (James Free), both of whom were rotating on the kidney service, began working on the magic hydration formula. Initially they made a mixture of 5 percent glucose with water with small

amounts of sodium and phosphate in a liter of fluid. They then filled four cups, toasted each other, and took a sip, or in the case of Dr Cade, a large gulp. Immediately they gagged, and Cade vomited as the taste was particularly bad. After he got home, Mary Cade, Bob's wife, suggested that the flavor might be improved with lemons, and the next several days they experimented by adding lemon juice as well as the sweetener cyclamate, finally developing a drink that was not only tolerable but had a pleasant taste.

They went back to Coach Graves to test the hydration drink for his team, and that weekend the LSU team[12] was to play the Gators. Graves was not ready to give the drink to his varsity team but suggested that they give the drink to the freshman team on the day before when the freshmen played the B squad. It was a tradition for the B squad to play the freshman team the day before big games, and it even carried the name of the "Toilette Bowl", and so Cade and his team prepared between 50 to 100 liters of the lemon-flavored drink for that day.

The freshman, as underdogs, were given the drink, whereas the B squad continued with their usual hydration of water with or without salt tablets. During the first half the B squad dominated, making several touchdowns with none scored by the freshman team. But in the second half things reversed, and the freshman teams scored 9 touchdowns while the B squad had none. At the end of the game the B squad was exhausted, but some of the freshman team continued to want to play.

Coach Graves was so impressed that he asked Bob to make another batch for the LSU game the following day.

That night the four musketeers (Cade, Shires, De Quesada and Free) met again in Dr Cade's laboratory to make another 100-liter batch only to find they were short of premium grade glucose. At that point Dewayne Douglas showed up and opened up the other laboratories so they could "borrow" the glucose from other labs. By 10 pm they had made the drink, and they retired to a local brew pub accompanied with their special drink stored in large glass jars.

The next day was extremely hot, with temperatures reaching 102 degrees Fahrenheit. The first player they gave the drink to liked it, but the second took a gulp and said it tasted like piss

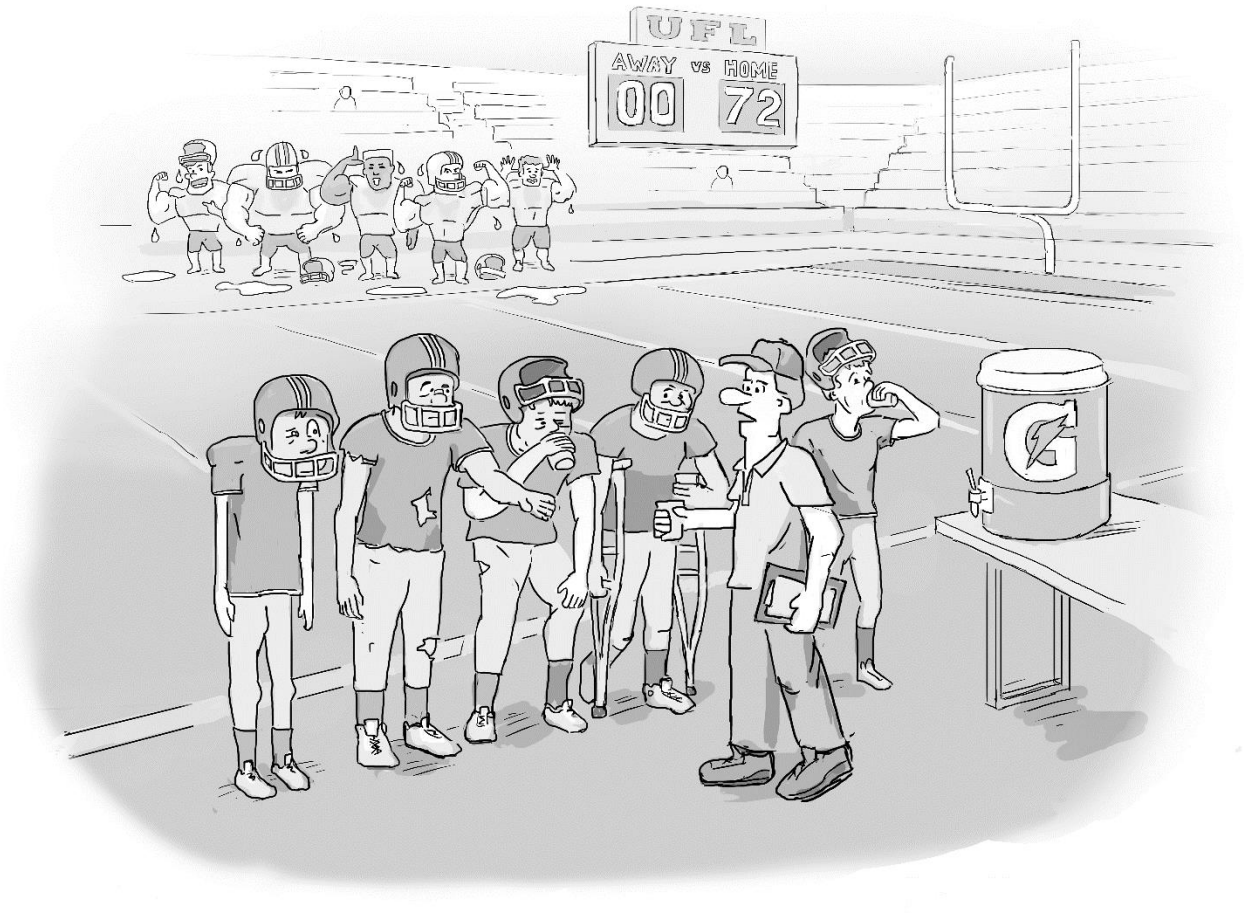
[12] Louisiana State University

and then poured in over his head. As Dr Cade wrote, "since one of our goals was to keep his body temperature down, I, though taken aback, nevertheless thought that pouring (the drink) on his head was beneficial even though it was not the most effective way to use it."

LSU took an early lead and was winning 13 to 0 at half-time. Both teams, however, seemed exhausted. Seeing this, and recalling how the freshman team did the day before, Graves called over to Cade "Bring out the drink." A major change occurred in the second half, and the Florida team came behind to win 14-13 in the final minutes.

Graves became excited by the drink, and asked for it for all of the remaining games. Jim Free then came up with the name of Gatorade. The drink was again used in 1966 for the games, leading to a story by Neil Amdur in the Miami Herald of the powerful effects of the new drink. His story was picked up by syndicates throughout the world, leading to great publicity about Gatorade.

Subsequently, the group decided to commercialize their drink. The University initially showed no interest since it viewed the drink as a type of Kool-Aid®, so the team worked on their own, eventually persuading Stokely-VanCamp in Indianapolis to market Gatorade as the first sports drink. Soon it was also found to be very helpful for treating children and people with diarrhea or other illnesses associated with dehydration. The drink subsequently was bought by Quaker Oats, and then Pepsi. One of the most important aspects was that its royalties were tied with its name (trademark) rather than by patent, and hence the royalties continue in perpetuity. Today some royalties also come to the University of Florida, amounting to more than 70 million dollars to date. Indeed, one of the first things I did as Head of the Kidney Division was to throw a major party to celebrate Cade and the other inventors and to heal any remaining wounds between the University and the Gatorade inventors.



Go easy on them, Boys. They have had a hard day.

I should mention that Dr Cade invented many other things as well. For example, he developed a device so women can urinate standing at a urinal (I still have one that he gave me). He was also concerned about the frequency of concussions in college football and thought he might be able to develop a better helmet. He noted that woodpeckers would bang their head all day long, but seemed to be protected because they had a higher among of fluid that existed between the skull and brain. Based on this, Cade developed a hydraulic helmet in which a network of mini-bags of oil formed a cushioning layer inside the football helmet. He told me that he wore a prototype and was being interviewed about it, when he challenged the announcer to hit his head with a helmet. When the announcer lightly tapped the helmet, Cade asked him to hit harder. The announcer then whacked Cade in the head, and it was enough to break the bags and the oil rushed down his face, scaring the announcer. That ended the helmet idea. He also developed a drink to block hangovers that was actually marketed for a while.

Cade always thought outside of the box. He was also very generous. I remember one time when he and I were at a cheap Mexican restaurant and the total only amounted to 20 dollars. Cade placed a one hundred dollar bill with the receipt and we both walked out, only to have the waitress run out and tell us he had made a mistake and had left too much. When he smiled at her and told her it was her tip, she cried in front of us. This is what kind of person he was.

Lessons to be Learned

If there is one characteristic that marked Bob Cade, it was that he was not tied down to rules. While at times this got him in trouble, his free spirit also gave him the vision to push the envelope and to see what others had not seen before him. It must be remembered that sports drinks did not exist before Bob Cade. In his case, his key insight that glucose and salt must be given together preceded his observation, but the two timed closely together. What did mark Bob and Dana were their scientific precision in figuring out the severity and types of water and electrolyte loss that was occurring in the athletes. The magical benefits of Gatorade in the sports arena carried the impact that was necessary to make the drink a success. I can also attest, that, while I am not a fan of soft drinks that contain much more sugar or high fructose corn syrup, I am convinced that

the benefits of Gatorade in the sports world and among those suffering from dehydration is quite significant, and a bottle is by my side whenever I get sick.

Knowing how Cade loved poetry, I end this chapter with a poem by Emily Dickinson that exclaims the virtue of being open to possibility. It was also a favorite poem of my mother's.

"I dwell in possibility,

A fairer house than Prose,

More numerous of windows—

Superior for door

Of chambers as the cedars

Impregnable of eye

And for an Everlasting Roof--

The gambrels of the sky"

Chapter 5 That Lets You Follow Your Instincts and Think Outside the Box

"When I was young, I observed that nine out of ten things I did were failures. So I did ten times more work." *George Bernard Shaw*

One challenge in discovery is to know when to give up and when to persevere. Success usually requires persistence. But if the experiment continues to fail, is it because your idea is wrong, or that you just need to keep trying? How does one decide? Is it a failure to stop trying, or is it wisdom? Likewise, even if the studies are not failing, sometimes something more interesting may show up. So how does one side when it is time to "jump ship" on one project and do something else?

The Case for Perseverance

By the early 1900s, it had been discovered that many infections were caused by small invisible creatures called bacteria. While normally invisible, they could be visualized using a microscope. Others had been able to grow colonies containing millions of bacteria on culture plates, and even to mimic human infections by injecting the bacteria into animals. Thus, it is not surprising that with the discovery of these living bacteria, there was a major attempt to find ways to kill them.

One influential scientist of the day was Paul Ehrlich, a German physician who had developed several different ways to stain the bacteria using various dyes. Ehrlich had also become famous when he developed the first effective compound for treating syphilis. The drug, salvarsan, contained arsenic and had lots of side effects, but it did kill the bacteria causing syphilis much better than giving mercury, which was one of the original treatments.

Ehrlich often talked about the need to find a "magic bullet", that being a drug that might kill the bacteria without being toxic to man. Based on his work with dyes that would be taken up by bacteria, he hypothesized that the magic bullet would be a dye that would preferentially bind to the bacteria and then kill it, thus ridding the world of these horrible infectious diseases.

One company that was listening to Ehrich was Bayer, a German company that made aniline dyes for clothes. In 1890 Bayer had introduced a drug for fever known as aspirin (acetylsalicylic

acid) that had been derived from the bark of a tree. They were now interested in expanding the medical business. and the idea that one of their dyes for clothes might represent the magic bullet to kill bacteria led them to invest in a whole new facility that would be dedicated strictly for testing the various dyes to see if they could function as antibiotics. For this purpose, they hired Gerhard Domagk.

Domagk was a physician on the faculty of the University of Munster. In 1927, just 6 years after finishing medical school, he was appointed as Director of Bayer's new Institute of Experimental Pathology and Bacteriology located near Cologne. Here his mission was test hundreds of dyes for potential antibacterial properties, first by seeing if they stained bacteria on a culture plate (thereby demonstrating a specific affinity of the dye or the bacteria), and then by actually injecting the dye into mice to see if he could protect them from infection.

Every day he would inject one group of mice with a dye, and leave the other group as a control. He would then inject lethal doses of streptococcal bacteria into all of the mice. Each day the experiment ended the same way, with all of the mice in both groups dying. It was quite depressing as nothing seemed to work. In fact, he carried out these monotonously depressing studies for 5 years. Then, on the morning of December 20th, 1932, he arrived at the laboratory to discover that all of the 12 mice that had received a particular dye the night before had survived, whereas all 14 controls died. "We stood there astounded….as if we had suffered an electric shock."[13] It seemed like a miracle, and when he repeated the study, similar results were obtained.

Immediately the company made everything top secret as they scrambled to get patent rights and to learn more about the dye. Specifically, the dye was called protonsil rubrum, and had been used as a red dye to stain leather. Its real benefit, however, was that it could kill the *Streptococcus* bacteria. This was a bacteria that could cause severe skin infections (such as cellulitis), throat infections (the famous strep throat), infections of the heart valve, and fever and sepsis in pregnancy. Indeed, in those days strep throat could worsen and spread, and even occasionally be fatal. Of all things, Domagk's six year-old daughter, Hildegard, was strickened with a severe streptococcal infection when she inadvertently punctured her hand with an embroidery needle. The infection began to spread up her arm with high fevers, and the lymph nodes in her armpit became

[13] Quoted from The Forgotten Plague by Frank Ryan, Boston, Little Brown ,1992 and also in Happy Accidents by Morton Meyers, Arcade Publishing, New York, 2007.

so swollen and infected that they had to be lanced multiple times. The family physician wanted to amputate the arm, but Domagk refused. Domagk decoded to take some protonsil home and treat his daughter secretly, and within two days her fever broke. With repeated courses her infection finally resolved and her arm was saved.

Unfortunately for Bayer, it was determined that the active ingredient in protonsil was not the dye itself, but rather a chemical called sulfanilamide, a substance that had been previously produced in 1908 by a French Group. Hence no patent rights for the active part of the drug could be claimed. Nevertheless, it took a few years before the first paper was published (in 1935) and before the first clinical trial reported (1936). This was followed by numerous studies, including one in which the use of sulfanilamide was able to control a meningitis outbreak in the French Foreign Legion stationed in Nigeria, dropping the mortality rate from 75 percent to 11 percent. The active form of the drug was even used to save the son of President Franklin D Roosevelt in December, 1936 when he was diagnosed with a severe case of tonsillitis.

Similarly, at Queen Charlotte's Hospital in London, a medical student, Meave Kenny, and his attending, Leonard Colebrook, were the first to treat women who had developed serious bacterial infections during childbirth. These infections resulted in fevers as high as 104 degrees Fahrenheit or more and were associated with a high mortality. When the patients were given treatment, mortality fell three- to four-fold. The drug could also kill other types of bacterial infections. Domagk, who had lived from failure to failure, now had the first world class antibiotic to be used in the clinic, and he was awarded the Nobel prize for this achievement in 1939.

I am not sure I would have been able to work for 5 years with repeated failure, so I think Dogmagk was a special type of individual. I would have certainly jumped ship simply from boredom. But in retrospect, his instinct was right. Not only did he get the world's first antibiotic, but he used that antibiotic to save his daughter's life when she became ill with a bad infection.

There is a story, that as far as I can tell, has not been validated, but it has been said that the world chess champion Capablanca was asked why he could win so often, and what was his trick. In particular, when Capablanca evaluated a chess position, how many moves ahead would he think? Capablanca replied, "Only one. But it is the right one." Now I know that this would have been a witty response that was not necessarily true, but it seems to me that he was trying to make

a different type of statement. Trust your instincts. Do what your soul tells you to do. And frankly, Domagk did pretty well!

While Domagk persevered, sometimes it may be better to "jump ship", not only if the current studies are failing, but also if something more exciting shows up. For example, Peter Agre, a physician at Johns Hopkins University, had been studying red blood cells and their specific proteins when he identified an unknown protein during his studies. He became intrigued with this new protein and began to study it rather than his project on red blood cells. His work took him out of his field, but he eventually identified that protein as being part of the 'channel' by which water moves in and out of cells. To discover how water gets in and out of cells is incredibly important when it comes to the basics of life, and Agre received the Nobel prize in 2003. I once had the opportunity to meet him, and when I asked him what made him decide to study the other protein and to change his research direction, he answered with a smile, "it must have been ADHD [attention deficit hyperactivity disorder]".

This seems a bit random! My guess is that Agre followed his instincts. And that is my recommendation as well. Follow your passion. Let your enthusiasm guide you. Be willing to have a little bit of Indiana Jones in you. Be willing to move into territories you might not be that comfortable with. Let me give you a personal example, one in which my plans switched halfway through my experiment.

The Purple People of the Andes

"You're staring at me," the old Dean said to the medical student, who immediately cringed at each word.

"Oh no, Professor Monge, I am not staring, not at all". The student looked away so she did not have to look at him in the eyes.

"I know what you are thinking, you are thinking that I am old, *very* old."

The student turned pale as a ghost and stammered, "No, Dr Monge, no, you are not old."

Monge smiled and said, "Yes, and you are right. And do you know why? Because mummies do not age."

A number of years ago, while I was at the University of Washington in Seattle, I obtained a grant to study the types of kidney disease that were in Peru with two physicians affiliated with Cayetano Heredia University in Lima (Dr Abdias Hurtado and Dr Elizabeth Escudero). The study was based in Lima which is on the coast, and so did not explore the types of kidney disease that were present at high altitude. However, Jacki Pando, a medical student working with Abdias, had just gone to a remote community high in the Peruvian Andes, where she went door to door asking the residents if she might test their urine. I imagine this must have been seen as an unusual request by the people she met, but nevertheless she succeeded in testing over 100 people. When she returned to Lima, she had the startling finding that one in ten of the people had excessive amounts of protein in their urine, which is a sign of early kidney disease. One potential explanation could relate to the low oxygen in the air that occurs as we go to higher altitude. A low oxygen due to the "thin" air could make the kidneys vulnerable to damage.

The data was interesting enough that we designed a study with the leftover funds we had. We picked Cerro de Pasco, a small mining community situated at 15,000 feet altitude, as the town had a small research facility that was owned by Cayetano Heredia, one of the main universities in Lima. Indeed, it was a research facility that had been maintained since the 1920s when a Peruvian physician, Carlos Monge, described a rare disease that now bears his name.

The red blood cells in everyone's blood increase in number with altitude in response to the low oxygen state. However, Monge noted that some people living in Cerro de Pasco developed an exuberant increase in the number of red blood cells. When the red blood cell increases too high, the skin turns dark red, and then almost purple, especially in the face and hands. The high concentration of red cells slows the circulation, increases the blood pressure, and can cause headaches and even strokes. Treatment is simple—remove some of the blood, allowing the circulation to be normal once more. Unfortunately, the low oxygen at high altitude continues to stimulate the production of blood, and so the disease rapidly recurs. While moving to sea level can lead to disease resolution, most individuals suffering from Monge's disease did not want to move as it meant leaving their families. As a result, they often live a shortened life treated by intermittent bloodletting until they finally succumbed from their disease.

The cause of Monge's disease, or *chronic mountain sickness*, was not known. As mentioned, everyone will have their red cells increase if they move to high altitude. However, this

response was much greater than expected and occurred in about 15 to 20 percent of people in Cerro de Pasco. It was also described in other towns in the Andes. The few experts who had studied the disease thought that it might be genetic, as it was not seen in sherpas living at high altitude in the Himalayan mountains. But no one really knew.

Anyway, we wanted to determine if chronic kidney disease was occurring at high altitude, and Cerro de Pasco was an ideal site because of the facility. We decided to study individuals who had lived in Cerro de Pasco for many years—and because the facility catered to subjects with Monge's disease who would come to have be intermittently bled, we also decided to investigate whether subjects with Monge's disease might have kidney disease. Finally, we included a study of Peruvians who lived at sea level that we would take Cerro de Pasco so they would be studied after acute exposure to high altitude. This way we could see if there is a difference in the degree of kidney disease based on whether you lived at high altitude chronically or if kidney injury could occur with rapid ascent to high altitude.

Preparations were made, and we brought together medical students, nurses, and physicians from both Seattle and Peru. Because I was not an expert on high altitude medicine, we were joined by Rob ('Brownie') Schoene, a friend of mine from the University of Washington who had climbed Denali and Everest but was most famous for trying to understand acute mountain sickness by having himself voluntarily bronchoscoped on a mountain top in the Alps.

The whole study was to be performed in one long weekend adventure. We would begin by examining 25 subjects living in Lima (which is at sea level), and that evening we would all take a bus up winding roads to Cerro de Pasco. We would bring with us oxygen tanks and medications to treat anyone who would get acutely ill from going to high altitude so quickly (such as headache, nausea or shortness of breath). We would then restudy the individuals we brought with us from Lima, and also test 25 Peruvian men who lived in Cerro de Pasco and had adapted to the high altitude setting, and 25 of the 'purple' men from Cerro de Pasco who suffered from chronic mountain sickness.

The night before the study began, our research group was invited to the house of Carlos Monge Cassinelli, the Dean of Cayetano Heredia Medical School and the son of Carlos Monge. Cassinelli was quite old himself, but remained spry and curious, and he had been a kidney specialist

as well, and so he wanted to wish us success on the trip. It was a beautiful evening and his home was filled with art and antiquities. Casinelli also had a great sense of humor and surprised the medical student with his joke (see earlier). But the most striking thing was that, at the end of the night, he wished me and our research group luck on our expedition, and as I was leaving, he gave me a book he had written with his father. I thanked him and tucked it into my bag.

An Expedition to the Andes

The next day our team spent all day evaluating the volunteers who had signed up in Lima, and that evening we all got on a bus to take us up the mountain to Cerro de Pasco. The bus driver was quite large, and his face was so fat that it looked like he could not see. He would hum as he drove, and I swear he looked like he was sleeping. I became nervous as the roads were narrow and poor, there were no guard rails, and the "plunge", if we were so unlucky, would be a thousand feet or more. The bus was so wide that there was not much space for oncoming cars, and sometimes we would come around a bend and find a llama or sheep. However, when I looked at the others in the bus, they were all happily sleeping!

Because I could not sleep, I pulled out the book Monge had given to me and read about the work he did with his father on the purple people. The premise was that the disease resulted from a maladaptation to living at high altitude, and that they simply responded to the thin air by making too many red blood cells. However, as I read the book, I found that the father and son team had noted that the disease was common in some high altitude communities, such as Cerro de Pasco, but not others. For example, chronic mountain sickness was not that common in La Paz, Bolivia despite it being at 12,000 feet altitude. Furthermore, chronic mountain sickness had been observed in communities with an altitude as low as 9,300 feet. So altitude was not the critical factor. But there was one striking finding. All of the communities where chronic mountain sickness was common were mining communities.

Of all things, in the prior months I had been studying how a low oxygen state might cause kidney disease. From my reading I was aware that a specific heavy metal, cobalt, could activate processes similar to what occurs with low oxygen, including the stimulation of blood production. A few months before, Ashley Jefferson, a research fellow working with me, and I had actually

discussed the possibility that cobalt could be involved in the purple people syndrome. However, reading the book on the bus in the middle of the night made me realize that this might be much more likely than we had thought.

We arrived in the early morning, just as many of the miners were leaving for work. The town was built around a large open pit mine, and there are also mines nearby. As I stepped off the bus, I could see a striking finding. While many people looked normal, there were occasional individuals with purple-red faces and hands. One could also see children who were developing the disease. Some also looked healthy, as their lips tended to be crimson red, with bright pink colors to the cheeks. But over time, they would develop the purple maroon. I remember in particular the two waitresses that served us lunch that day. Both were in their early 20s, but one was dark maroon and the other had normal color skin.

We went to the clinic and began examining subjects. It was not the best setting, as there was no heating and we were even limited without hot water on Sunday, but we managed to examine our subjects and collect blood samples. It was after we had examined a dozen or so subjects that one young man walked in whose face and fingers were not only purple, but almost purple black. He had volunteered to enter the study, but he also had chronic headaches and ringing in his ears. When we tested his blood, we found that it was the highest ever reported in the world, with 91 percent of the blood being from the red cells. We immediately arranged for him to have his blood drawn.

I continued to be bothered by the idea that these people might be suffering from cobalt poisoning, as did the rest of our team. As the purpose of the study was to evaluate their kidney function, my team had to continue with the study. However, since I was the leader, I decided to excuse myself and investigate the cobalt idea further. One of the key findings were that the volunteers entering the study did not themselves work in the mine. Therefore, it seemed like the source of cobalt, if it were present, was probably from local water or food that had been contaminated by wastes from the mine.

Given that my ability to speak Spanish was poor, it was important to find someone to help me. Luckily, one of the volunteers who came on the bus with us was actually a friend, Mario Romero. Mario and two other volunteers agreed to take me to the water treatment plant. Here we

met with the officials who told me that the slag water from the mines went by canals into the local river. In turn, the drinking water came from the same river. Furthermore, the mines were primarily producing silver, zinc and lead, and they had monitored levels of these in the water. However, they were not aware if cobalt was in the mines, nor had they ever tested for it.

Cobalt is a bluish metal that is often present in only small amounts in mines. The German word for cobalt is "cobalin", and is the word goblin originates from, as cobalt, like goblins, is found in the deep recesses of a mine or cave, Cobalt, and to a lesser extent nickel, have been

The slag water from the mines drains into canals that then enter the river. In turn, the drinking water also comes from the river where it is brought in by pipes. We obtained water samples at multiple sites– including climbing over barbwire fences to get samples from the mine itself.

known to increase the red cell response to low oxygen conditions. Nevertheless, cobalt poisoning is considered rare. However, in the 1960s, before its problems were fully recognized, cobalt was added to some commercial beers to give it a bigger "foam". Unfortunately, this was associated with a syndrome with high red cell counts and heart failure.

Equipped with a map, we went to the mine and stared at the reddish slag water through the barb wire fence. We could see that the water was draining into canals that would take the water to the river. Knowing that the owners of the mine would not like what we were doing, we realized we needed to sneak into the premises so we could test the slag water. Although all of us were game for the adventure, Mario went over the fence first and came back with the dirty water.

We followed the canal of mine water as it coursed through the town to the river. Often we could see children playing in the water, or women washing their clothes. Eventually we reached the river into which the mine water entered. Only several hundred yards away we could see the large water pipes bringing the river water back to the town. But there was one important thing—the drinking water exited the river upstream of where the wastewater entered the river! Nevertheless, we tested the water as it entered the pipes, and also at various sites in the city.

When we returned to Seattle, we sent off blood samples to a laboratory to have the cobalt measured. Everything was done blinded. When the results came back, we were shocked. Cobalt levels were only detected in those with the highest blood counts, and the person with the highest blood count ever recorded in the world had the highest cobalt level. The mine water was also rich in cobalt, but strikingly the drinking water was not. Although we did not test it, we suspect that the cobalt poisoning in the population might be due to eating of fish in the river, as cobalt concentrates in fish. We subsequently published our discovery in the Lancet. And yes, we also found that kidney disease was increased at high altitude, so the original study was also positive.

Over the years, the local mines were forced by the government to improve in their disposal of wastes. The local river also became so contaminated that fishing is no longer allowed. And when we returned to Cerro de Pasco a few years ago, we no longer could find subjects with severely elevated red cell counts. Only a few individuals with modestly high red cell counts had elevated cobalt levels in their blood. Hence, the cobalt poisoning of this population has largely resolved. Mild chronic mountain sickness still exists, and may in fact be driven by genetics. However, the purple people syndrome has been resolved.

About 5 years ago I had the opportunity to go to Tibet, where I told this story to local Tibetan physicians. Blood counts in Tibetans are lower than of natives living in the Andes, and chronic mountain sickness is very rare in this part of the world. But they did tell me there was one exception. There is a remote area where they see individuals with high red cell counts, and it is an area where there is mining for nickel. Nickel is the other metal that can increase red cell counts. So somewhere in the Himalayas lies another disease to be discovered!

Chapter 6 The Trick is to Overcome the Barriers..

"Discovery consists of seeing what everybody else has seen and thinking what nobody has thought." *Albert Szent-Gyorgyi* (the discoverer of vitamin C)

"There are only two things one needs to know in physics", my high school physics teacher once said, "and that is that force equals mass times acceleration, and you can't push on a rope." While he was being funny, he was following a basic teaching tenet, which is to make things black and white.

I learned this myself when I would teach medical students as a faculty member of the kidney division at the University of Washington. Following a lecture on a general topic given a by one of our professors, there would be "break-out" sessions in which medical students would go to various rooms where our faculty, fellows in training, and occasionally physicians from private practice would then discuss specific cases. Each of us would have about 10 to 15 medical students per group, but after a few of these sessions, I would notice my group getting smaller, and this happened to other teachers as well. I assumed that the students were becoming more comfortable about the topic as class proceeded, and so weren't attending class. However, my boss, Dr William Couser, noted that the students were flocking to the room of one particular individual to the point that the room was overfilling. What bothered both Bill and me was that that teacher was a physician who was in private practice, yet his teaching was loved much more than the rest of us who were University faculty and devoted to teaching.

And so, one day, when I did not have to teach, I went to the back of his class to figure out why he was so popular. He would say something like, "There are only five causes of xxx… and once you have this memorized then these are the four things you need to do. First, you….". In essence, he made it very easy to learn as he presented science as if everything was known, everything had a particular way to be handled, and everything had one specific treatment. There was no "but if's" and nothing grey.

When it comes to learning, it is easiest when things are black and white. It is much harder to learn information if it is 'fuzzy-wuzzy'. Many view science as a definitive discipline, one where

the rules are absolute, and it is easy to carry this over to studies of biology and medicine[14]. We like to categorize. This is especially true for textbooks.

But the truth is that what we don't know is much more than what we do know, at least when it comes to medicine. We would like to believe that science is absolute, and it probably is, but what we are taught is not 'absolute' science, it is the 'working' science. In essence, it starts when someone made some observations, or perhaps performed some experiments, and then published their work. In the paper the individual (or individuals) summarize their findings and make some type of interpretation of what the data shows. The title of the manuscript is used like an advertisement to attract readers, and so it often focuses on the big finding, or often on the impact of the finding. This 'impact' really relates to how the author interprets the observations. In turn, it is this interpretation that is then engrained into the mind of the reader. Eventually this interpretation is what is put in the textbook and is taught to our students as if it is an absolute truth.

Years go by, and more data is published, and some of the new findings may not be consistent with the original interpretation. These 'anomalies' are initially ignored and brushed-off, and are viewed as incorrect, of poor quality, or are considered as coming from unreliable sources. If they persist despite attempts to bury them, then they become 'exceptions'. Finally, someone who is often new to the field realizes that, while the *data* from the original study was correct, the original interpretation was wrong and needs to be modified. That individual then presents his or her new idea that explains the original data, as well as the newer "anomalous" findings. The leaders in the field, however, are often the ones that made the original interpretations, and they often view this new idea as a breach to the original hypothesis that often represents their life's work. Since they represent the 'Establishment' with the associated leadership and seniority, they almost always shoot down the idea and castigate the lone individual who is challenging their authority. That often ends the discussion for a decade or two, until finally the senior leaders die out and the new generation that is more open can adapt the new interpretation, which now takes over the field until the next cycle begins. Mark Twain said, "Whenever you find yourself on the side of the majority,

[14] Physicians, especially in the past, would give complicated names in Latin to conditions that made it outwardly sound like the diagnosis was definitive. I am not sure if this was to make the physician feel more self-important or the patient more confident in his or her care. My father used to laugh about this, and say. " I saw a patient today and the diagnosis was puzzling. I finally realized it was another case of idiopathic erythematous pruritic dermatitis medicamentosa." I would nod approvingly. Doctors are so smart! But what it means is a red, itchy rash of unknown cause that may or may not relate to a medication.

it is time to pause and reflect." When we think that what we are taught is gospel, then our convictions create prejudices that prevent us from moving the field forward.

I am not telling you never to read a textbook, but rather that we need to realize that what we are taught is not absolute, and we may need to be a bit more open in how we approach things. This is not just for science, but for everything in life. Twain seemed to note the distinction between learning a field and reading only textbooks. "I've never let my school interfere with my education," he remarked. Similarly, Winston Churchill also said, "I am always ready to learn but I do not always like being taught."

Let me give an example of how incorrect science can become dogma. It is well known that our genes are carried in our DNA, which is kept in chromosomes in the nucleus of the cell. Back in the 1920s the geneticist Theophilus Painter figured out that males carried an X and Y chromosome while females carried two X chromosomes. This seems like a fairly significant discovery! He also counted the overall number of chromosomes and declared that humans have 48 chromosomes. Admittedly, his original paper that was published in 1923 stated that it was difficult to be sure that the number was 48. But no one questioned Painter, and for the next thirty years, multiple groups confirmed that humans had 48 chromosomes. By 1954 Dr Leo Sachs from the Weizman Institute wrote "the chromosome number of 48 in man can now be considered an established fact". Then, in early 1955 a husband-wife team of Eva and Yngve Melander found only 46 chromosomes in human cells that they were studying, but they thought there must have been an error, possibly due to "problems with their chromosome preparation" and hence did not publish their findings. In essence, the science was in stone—humans have 48 chromosomes.

This all changed later that year when Jo Hin Tjio and Albert Levan published a paper in which they argued that the true number of chromosomes in humans was 46. It seemed heretical, but their presentation was so convincing that they were able to change the world view. What gave them the bravery to challenge the dogma likely related to the convincing nature of the data. However, Tjio (the scientist who did the experiment) had a history of having been tortured and imprisoned by the Japanese during World War II, and so may not have been afraid to challenge the towers of academia.

I have called this process, "the lemming phenomenon"[15]. Lemmings are mouse or vole-like animals that typically live in the tundra in the Arctic. At various times they can go through rapid increases in population, resulting in mass migrations. It got into the literature that lemmings follow each other with such 'blind faith' that they follow the leader even if it means jumping off a cliff. This was reinforced in a 1958 Academy Award-winning film produced by Walt Disney, called *White Wilderness*, in which lemmings were shown rushing to a cliff and then jumping to their death. However, later it was found that the filming was staged, and that the lemmings had been transported to the cliff by truck, and then forced to jump off. Indeed, recently the idea that lemmings actually do this behavior has been questioned. So, the 'blind faith' is not that lemmings will follow each other even if it is to their death, but rather because we blindly believed that the story is true. Once something is accepted, people tend to believe in it even if the new science says otherwise.

There are other ways the science we are taught can lie. One major area is statistics, which is really about looking at the odds of something happening based on a population, but may not be valid for the individual. The method often assumes that the population being studied are all similar, but sometimes the individuals may look outwardly similar but may actually have different conditions that respond differently depending on the treatment. There is also a crazy statistical method which determines if something confers a risk for a disease independently of other known risk factors. Scientists often falsely assume that a true risk factor has to be independent of other risk factors to be causal, which of course is not true if the risk factors are dependent on each other. Indeed, I used this lousy method to argue that it was not John Wilkes Booth who assassinated Lincoln, but rather it was done by a bullet, as if there was no bullet, it would not have happened[16]. As Mark Twain said, "There are three types of lies: Lies, Damned Lies, and Statistics".

[15] Johnson RJ. Finding the truth: blind faith and the lemming phenomenon. J R Soc Med. 2018 May;111(5):175-176.

[16] Johnson RJ. Finding the truth: multivariable analysis and the assassination of Abraham Lincoln. J R Coll Physicians Edinb. 2018 Jun;48(2):153-154.

The Advantage of Being New to the Field

While we would think that the breakthroughs in science should come from the experts in the field, they are often wed to the established thinking and approaches. So, ironically, breakthroughs are often led by those new to a field (such as students or individuals in training) or from experts from other fields who are looking at the question for a first time[17]. Experts who are convinced they are right often do not keep up with the literature as they feel the situation is proven. In contrast amateurs tend to be less read and to have less knowledge, and this translates into having a more open mind. They are more likely to come up with solutions that are outside the box, and also more likely to make associations that might have been known but had been largely forgotten.

A great example of the power of being an amateur relates to William Bosworth Castle. In the early 1900s a type of anemia was extremely prevalent throughout United States and Europe. Unlike the more common iron deficiency anemia present from heavy menstruation or other types of blood loss, this anemia had a particularly "pernicious" aspect. Not only would it present as fatigue, like iron–deficiency, but it could progress, leading to generalized weakness, with an enlarged and painful red tongue, sores on the edges of the mouth, brittle nails, and stomach upset. The skin would become a pale yellow, and over time there is a loss of balance, requiring the individual to slap down their feet as they lose sensation in their legs and feet. Memory slowly worsens, there is a general "foggy thinking" and eventually dementia sets in. Death was inevitable. Indeed, it had taken the lives of many famous people, including Alexander Graham Bell in 1922 and Annie Oakley in 1926. The cause of pernicious anemia was unknown, but a curious observation was that these individuals appeared to lack the normal amounts of acid in their stomachs.

Enter William Bosworth Castle, who went to Harvard Medical School in 1917. A good student, he nevertheless flunked his rotation in hematology during the second year as he had trouble counting red cells with the counting chamber. Despite this mishap, he graduated from medical school and after his residency he joined the clinical research unit in 1925 at the Thorndike Memorial laboratory at Boston City Hospital where he decided to do research, as you may surmise, in hematology.

[17]The advantage of the amateur over the expert in the discovery process is discussed by Thomas Kuhn in his book, *The Structure of Scientific Revolutions*. 1962; University of Chicago Press. 1-172

One of the leaders at the Thorndike was George Minot, a scientist who had been rescued from diabetic coma only a year before because of the injection of insulin which had only been discovered a couple of years before by Banting. Minot was an expert on pernicious anemia, and Castle listened to one of his lectures in which Minot reported the exciting finding that the anemia could improve if the patients were forced to ingest large amounts (10 to 12 ounces) of raw liver. Following the lecture, Castle walked to the elevator, when he had an insight. If it was true that pernicious anemia patients did not make adequate amounts of gastric acid for digestion, what if he gave the acid back—could it help make whatever was in the raw liver work?

Castle became progressively obsessed with the idea and began to think how he might prove this. He then came up with a plan. He slept in a room near the kitchen that provided the food for the patients on the ward. One early morning, he snuck into the kitchen and took some raw beef patties from the refrigerator. I suspect he would have chosen liver if it had been available. He then swallowed the raw meat (about 10 to 12 ounces) and let it sit in his stomach for about 60 minutes. He then tickled the back of his throat with his finger, causing a gag reflex that led to him vomiting up the half-digested meat. Carefully, so carefully, he added hydrochloric acid (HCl) to the mix until the pH was between 2.5 and 3.5, making it similar to the levels of acid present in the stomach. He then let it incubate for 6 hours at room temperature, and then passed the digested remains through a cheese cloth, collecting the brownish fluid in a flask. He then neutralized the soupy mix with sodium bicarbonate so it was not so acidic anymore, and walked down to the wards where he found some patients suffering from the horrid disease. After telling them that it might help their anemia he placed a tube down the nose into their stomachs, and injected the brownish fluids.

Anemia can take time to respond, but it had recently been discovered that new red cells are slightly larger in size and can be distinguished from normal red cells, and to his great excitement, the special slurry could induce a response of these new red cells. He then proceeded with further studies and showed that neither gastric juice alone, nor the beef alone, could stimulate the response—only when he incubated the meat in his own stomach.

After several years, the cause of pernicious anemia was shown to be due to a deficiency in vitamin B12. The reason Castle's experiment worked was because the lining of the stomach produced a special protein that helped the vitamin B12 present in meats and other foods get absorbed (known as intrinsic factor). Patients with pernicious anemia had a loss of the cells that produced this protein as well as acid. Hence, they were susceptible to becoming deficient in

vitamin B12. The reason raw liver could overcome this is that the liver is extremely high in B12, and if enough B12 is given, then it overrides the need for intrinsic factor. Indeed, Castle went on to make an extract of liver in which the B12 was highly concentrated, and it even worked if it was injected directly into the muscle, which avoided all concerns about absorption in the gut. Today oral B12 vitamin is enough to prevent anemia even in subjects who have had their stomachs removed by surgery.

Castle's idea was new as there had been little thinking about the role of stomach acid in the disease, but moreover his 'mad scientist' approach to testing his idea is unlikely to have been thought about by the professors in the department. Of course, this type of study would likely not have passed if it had been submitted to a human subjects review board today. Nevertheless, it reflects well on the thinking of a young person new to the field, who seizes on an idea and follows it through, giving insight into the cause of a disease.

A Visit with Sherlock Holmes

It seems there must be something wrong if the experts are less able to make discoveries than the amateurs. After all, Sherlock Holmes was anything but a novice, and he obviously did well with solving mysteries. If only I could speak to him! Speaking of which, there have been times when I go to bed and dream I am in London back in the 1890s so I can consult with Sherlock.[18] So last night I went back in time, to London in the 1890s, and went to 221B Baker Street to once more talk to Sherlock Holmes and Doctor Watson.

Watson answered the door, and, as usual, was wearing his tweed coat and bow tie.

"Good day, Dr Johnson. Holmes will be pleased to see you. He is in the study". As we entered the room, it seemed more like a library, with books all over, and with some stacked high on the table. Holmes was smoking his pipe and was intensely reading a very old book.

"Aha, it is the Professor. I see you are here for another consult," Holmes said as he put the book down.

[18] Johnson RJ. Pro: Heat stress as a potential etiology of Mesoamerican and Sri Lankan nephropathy: a late night consult with Sherlock Holmes. Nephrol Dial Transplant. 2017 Apr 1;32(4):598-602.

I sat down across from him and was about to speak when Watson brought a plate of chocolates to me. Chocolates are my weakness, and I quickly took one. It also appeared to be a weakness for Watson, who seemed a bit more rotund than I recalled.

"Sherlock, I need your help. This time I do not have a case to solve, but rather a question I cannot answer. I am writing a book on discovery and have this puzzling observation. Why are the young and inexperienced often the ones that make discoveries as opposed to the experts who have devoted their careers to learning the subject? You seem to be proof that this idea is wrong, for you are the expert at solving mysteries, and certainly not an amateur."

"Johnson, experts can solve mysteries. But please, do not compare others to me. *No man lives or has ever lived who has brought the same amount of study and of natural talent to the detection of crime which I have done* [A Study in Scarlet]."

"The problem with the expert is that he thinks he is prepared, whereas the amateur knows he is not. Unfortunately, not even experts should assume they know their subject. For one should *never trust to general impressions, my boy, but concentrate yourself upon details* [The Adventure of the Blue Carbuncle]. *The trick is to always approach a case with an absolutely blank mind. It is always an advantage. Form no theories, just simply observe and draw inferences from your observations* [The Adventure of the Cardboard Box].

Experts can assist themselves by reviewing the literature on the topic, and separating the opinions from facts. It is common for the experts to confuse the two and *to twist facts to suit theories, instead of theories to suit facts.* [A Scandal in Bohemia]. And beware, *there is nothing more deceptive than an obvious fact* [The Boscombe Valley Mystery]. *What is out of common is usually a guide rather than a hindrance* [A Study in Scarlet]. And *never make exceptions. An exception disproves the rule* [The Sign of Four]. After I *gather the facts. I smoke several pipes over them, trying to separate those which are crucial from those which were merely incidental* [The Crooked Man]. Then I *balance probabilities and choose the most likely. It is the scientific use of the imagination* [The Hound of the Baskervilles]. *How often have I said to you that when you have eliminated the impossible, whatever remains, however improbable, must be the truth?* [The Sign of the Four].

At that time, the maid came into the room with coffee for each of us. "I know you would want another cup of coffee," Holmes remarked.

"How did you know I have already had coffee this morning?"

Watson intervened with a smile. “Even I am more observant than you. You have coffee stains all over your shirt.”

Indeed, when I looked down at my white shirt, my shirt had a large brown stain. I winced and drank the coffee in one gulp.

“Sherlock, thank you so much for your insights. It seems straightforward, but I know that this is an art that few can master.”

“No worries. *It is my business to know what other people don’t know* [The Blue Carbuncle].

I thanked Holmes, who nodded and went back to reading as I walked to the door with Watson at my side.

Watson turned to me as I was about to leave. “Do not feel bad. There is only one Holmes. I do have a suggestion, however. Just tell the readers your personal opinion. But be dogmatic, you will be more persuasive.”

“Let me guess. Did you also attend the small group class that was overfilled with students and that was taught by a physician in private practice who had answers for everything, even when there were no questions?”

“Exactly, Johnson. You may have a bit more of the detective in you than you think. Good luck with your book. The game is afoot.”

Chapter 7… to Make the Discovery

"Think left and think right and think low and think high. Oh, the thinks you can think up if only you try." *Dr Seuss*

So at this point in the book, I am supposed to tell you how you can become a discoverer, or how to become an inventor, or a more creative artist. Apparently the more dogmatic I am, the more you are likely to remember what I say. So should these be Johnson's commandments? No, this sounds too dogmatic. Johnson's rules? No, too school-like. Johnson's covenants? No, too religious. How about Johnson's recommendations? Perhaps too wishy-washy? Ah, forget it, let's go with recommendations.

While I would like to say that we should simply be like Sherlock Holmes, I keep realizing that few of us can follow in his footsteps. Even Holmes insists he is the only one that can do what he does. But there is another hero of mine whose viewpoint is great for those interested in discovery, and that is Winston Churchill. Churchill was the prime minister of the United Kingdom during the Second World War, and he made many statements aimed to keep the spirits of his people high despite being under constant attack. And the road to discovery requires similar survival tactics as being at war. So, in some respects, Churchill can be our mentor.

Let's look at Johnson's recommendations.

Attitude

"Attitude is a little thing that makes a big difference." *Winston Churchill*

Curiosity. Of all qualities, curiosity is the most important if you want to be creative. So how can you become more curious? The answer is to ask questions. When you ask questions, you may learn things you did not know, and it will stimulate more questions that will make you more curious—sort of a self-fulfilling prophecy. Asking questions breeds curiosity, while curiosity breeds questions. And when you get into this circle, that is how passions develop. And becoming passionate is the inner force that keeps you going, for making a discovery and getting it accepted

is not so easy. Best of all, becoming curious and passionate is something that takes no skill and is easy to do. The way to do this is to *just ask questions*.

Be Optimistic. There is a spirit to investigation, and it begins with a positive attitude. Churchill said, "A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty." When things are bad, do you want to curl up and hide, or be like the great Indiana Jones, and laugh, slap your leg, and then find some spectacular way to save the world? Getting someone to be optimistic is not so easy, however, but there are several other qualities that help, and the first step is to make sure you are having fun.

Being Playful. We have already talked about the importance of playfulness in helping create a relaxed, fun atmosphere that encourages open thinking. Robert Cade, the inventor of Gatorade, was the master. Being playful also raises the energy and makes people happier, and happiness makes people more optimistic and also more productive. My mentor, Bill Couser, taught me a long time ago that having fun events with the people you work with encourages more interactions, generates more fun, and helps generate new ideas and more productivity. When I was in Seattle, I would take my laboratory out for either a full day or half day of fun at least once a month. We would go to restaurants and cafes, or museums, or go skiing or sailing. The idea was to take a day off and play, while at the same time getting to know each other better, to develop stronger friendships, and to create positive attitudes. One day a researcher from another laboratory asked me, "How can your group be so productive with so many presentations and papers when you always seem to be taking time off to play?" My answer was simple. "We are productive *because* we take time to play."

Avoid Being a Perfectionist. When one finds something new, the goal is to study it until you are convinced it is more compelling than the way things are currently viewed. There are often hundreds of questions that come with a new idea or approach, and a perfectionist can be weighed down if they try to address all of the questions they can think of. This does not mean that you cannot address any question raised, but rather that the time element associated with addressing every question could potentially drag on for a very long time, and thus hinder you from presenting

your idea to others. The goal is never to fully prove your hypothesis, but just present a compelling case. Let the next generation dot the i's, cross the t's, or delete the paragraph.

Giving Yourself Deadlines. One way to fight perfectionism is to give ourselves deadlines and then stick to them. This is hard because we all say, "yes, that is a great idea to have a deadline, and sure, I can do it," but the actual fact is that we all hate deadlines and we hate sticking to them. As Douglas Adams wrote, "I love deadlines. I like the whooshing sound they make as they fly by." But there is an interesting finding, and that is, that if we actually do keep to the deadline, then the last day or hours before the bell chimes, many of us go into high power mode to get things done. And while relaxation is one way to let ideas fly, sometimes when we are under pressure we may find ways to pull a rabbit from the hat. An example relevant to me occurred during my final examination in my calculus class during freshman year at the University of Wisconsin. I stumbled on the last question (and there were only four) and had no idea how to solve it by calculus. Then I realized that the problem ended with "Solve the Question" and did not specifically say that we had to do it by calculus. I got the crazy idea that I could solve it by logic, and so I wrote out a series of "if this, then that" until I thought I had it. When the tests came back, the teacher began by stating that the last calculus question was difficult for everyone, but one person solved it by using a different approach. As Kurt Vonnegut wrote, "We have to continually be jumping off cliffs and developing our wings on the way down.?" Nevertheless, I was lucky that day. Most teachers are not so open to alternative strategies.

Developing Self-Confidence. Once you understand that you do not want to be a perfectionist, then you will realize that the goal is simply to get the science closer to the truth, and not necessarily identify the absolute truth. This requires acceptance of the idea that your discovery or new idea may also need to be altered in the future if new data arises that challenges it. Once you recognize that it is okay if your idea might be wrong and that this is not a disaster or the end of your career, then it will free you. So, if you are optimistic, having fun, and willing to be potentially wrong, self-confidence will naturally develop.

Bravery. Once you believe in yourself, yet willing to be wrong, then you are ready to play the game. If your goal is simply to move the field forward, then it easy to be brave. If you turn out to

be right, then there are no concerns, while if new data emerges that suggests you are wrong, you simply modify the hypothesis. Only be afraid if you are wed to the hypothesis so much that you yourself can't modify the hypothesis as new data emerges. Furthermore, recognize that if you are wrong, but you had a good hypothesis, you are still moving the field forward, as you helped rule out an idea that otherwise would remain on the list of possibility. Andre Gide, a French author who received the Nobel Prize in Literature in 1947, wrote "Man cannot discover new oceans unless he has the courage to lose sight of the shore." And Isaac Newton wrote, "No great discovery was ever made without a bold guess." And if Newton says guessing is ok, I think I can hold this argument!

Importantly, new ideas tend to jar the establishment. Recognize that there will be pushback if you have an idea that may challenge the field or if you are an artist and present a new viewpoint or style. But do not let this bother you---listen to those who have found themselves in similar situations and stand strong. Albert Szent-Gyorgi, the Nobel-prize winning biochemist who discovered vitamin C, wrote "If everybody says that you are wrong, then you are one step ahead. But there is one situation which is better still, when everyone begins to laugh about you, then you know you are two steps ahead." An even better example is how Niels Bohr, a Nobel laureate himself, explained how his views of Wolfgang Pauli's new ideas related to spin theory and quantum mechanics (and for which Pauli also received the Nobel Prize). "We are all agreed that your theory is crazy. The question which divides us is whether it is crazy enough to have a chance of being correct. My own feeling is that it is not crazy enough."

Perseverance. We have already talked about this, but developing a new idea requires perseverance. This only works if you continue to be passionate about your idea. And that goes back to being curious, asking questions, and then developing an idea.

A great example of an individual with many of these characteristics was Charles Darwin, whose discovery of natural selection and evolution may represent one of the greatest disruptive scientific breakthroughs of all time. He was not a great student, and in fact was frequently below average in his studies at school. But he was curious, playful, persistent, and observant. He especially loved everything in nature, and as far back as childhood would love to go for walks in the fields and woods by his home. One time he was on a walk when he spied two beetles he desired

for his collection, and he grabbed them with each hand. When he saw a third beetle, he came up with the clever solution of putting one of the beetles in his mouth so he could free a hand to grab the third beetle, only to have the one in its mouth go into a temper tantrum and secrete a bitter stinging liquid. My guess is that he did not get home with all three beetles!

It was because of this love of nature and his afternoon walks with a professor at Cambridge that the professor recommended him to be the naturalist on the HMS Beagle when he was just 22 years old. During that expedition Darwin made countless observations that led to formulating his theory of natural selection and evolution. It is true that it took him 20 years before he presented his hypothesis, so one could argue that he was likely not good with deadlines. However, his delay was due in part to his perfectionist tendencies to make the strongest argument possible, especially since the argument was so disruptive and heretical. Indeed, what finally moved him to present his work was when a younger colleague by the name of Alfred Russell Wallace sent Darwin a paper he had written that proposed the same concept. Darwin was gracious enough to propose that Wallace present this work alongside with Darwin's at the Linnean Society in London. Within the following year Darwin published his famous book, *Origin of Species*. I guess competition is not always bad, as it can encourage individuals to get their work out in a more timely way.

Don't Be a Jabberwocky. While presenting new ideas is always good, don't become overconfident, a zealot, or a narcissist who falls hopelessly in love with your own ideas. The Jabberwocky was a nonsense poem written by Lewis Carroll in the book, *Alice and Wonderland*, and probably has a different meaning for everyone. But for me, I define a jabberwocky as someone who doesn't simply present his or her ideas, but who is also consumed by them. These individuals continue to push their ideas into your face and follow you everywhere you go with the conviction that only they are right. The individual becomes trapped, closing off his or her mind to ideas by others. It is really about fanaticism. Our friend, Churchill, said, "A fanatic is one who can't change his mind and won't change the subject." This is being a jabberwocky. Look into my eyes, and repeat after me, "I promise not to be a Jabberwocky, I promise not to be a Jabberwocky." Then, click your heels three times (for good measure).

Preparation

Sherlock Holmes may be right that experts should be able to make discoveries as well as those new to the field, but what is the trick? I believe that the disadvantage of the expert is that they think they know what is going on, so they focus on what is currently happening and what is new. However, the problem is that what we have been taught is a mixture of facts and opinions, and they overlap so much that they can be difficult to distinguish. Thus, some of the ideas we think are correct may in fact reflect potential prejudices of those who were the leaders before us. But there are ways to level the playing field. One can be done from the armchair, and the other from the battlefield.

The Armchair Approach. While it is common to focus on all of the recent advances for a topic, there is incredible benefit reading the old literature on a subject. Churchill wrote, "The farther backward you can look, the farther forward you can see." The goal is to go back in time and to look at how current thinking on a subject developed, and to try to distinguish observations from interpretations. It is especially helpful to then look at reviews (such as by decade) so you can follow how the condition was viewed. Usually, the interpretations seemed logical at that time, but the trick is that we have the knowledge from today that can help us identify where the 'mistakes' were made.

I would like to digress here and give a personal example for how diving into the past can provide insights. Around 2004, the epidemics of obesity and diabetes were well entrenched and had been going on for decades. The cause was widely considered to be due to the overconsumption of food coupled with lack of exercise. One interesting aspect was that both obesity and diabetes were more frequent in Native American and African Americans. This led many scientists to suggest that these groups likely had some genetic predisposition for developing these conditions.

I decided to dive into the past and read the earliest reports I could find on diabetes.[19] Using search engines such as google,[20] I was able to find a paper published in the 1920s by Dr Haven Emerson, who at that time was the New York City Health Commissioner. He had become concerned because he found that diabetes had increased in New York City and was affecting

[19] This specific approach of diving into the history of diabetes was a method similarly used by the investigative reporter, Gary Taubes, in *Good Calories, Bad Calories*, as well as what I used in my book, *The Fat Switch*.
[20] In the field of medicine, this usually involves a search on an on-line program such as Entrez PubMed. I will go to the oldest article, pull it, and then look for references in that paper to diabetes, and then continue to pull the earlier articles until I find the oldest one I can. Believe it or not, this sometimes takes me to libraries (which seem to be rarely used these days).

approximately 25 people out of every 100 thousand. That sounds rare to me, but his concern was that it had increased by more than ten-fold from just a few decades prior. The study was very well conducted and came to the conclusion that diabetes was a disease of the rich, that it was rare in African Americans, and that it was strongly associated with sugar intake.

I decided to dive even deeper, I found an article by a French physician from 1880 who was one of the first to suggest that there were two types of diabetes, with one associated with being overweight and the other with being thin. Of interest, he noted the overweight form of diabetes was associated with sugar intake. I went farther back in the literature, and found a paper from 1683 that came from a Dr Blankaart in Antwerp which was the port where the Dutch East Indies company brought the sugarcane that was being brought in from Java. Blankaart wrote how obesity was becoming extremely common, as were dental cavities, and how it seemed linked to the importation of sugar. Now I even went farther back. Sugarcane was first cultivated in the Ganges River Valley, and one of the earliest and famous physicians was Sushruta who lived there. It was known that he was one of the first to describe obesity, first to describe diabetes, and also the first to describe what was likely coronary artery disease. Unfortunately, his writing was in Sanskrit, but I was able to find a 1910 translation of his book.[21] It was an enormous book, and there was no hope I could ever read this, but I was able to search using old, antiquated words that meant sweet, such as treacle. Using these words, I found that Sushruta also linked these diseases with drinking the sugary syrup from boiled sugarcane.

Soon I was able to find multiple references that showed that whenever sugar was introduced, that shortly thereafter diabetes would appear. For example, I read how Maimonides, a physician who lived in the 9th century A.D, had seen no cases of diabetes when he lived in Spain, but he saw over 20 cases in Egypt where sugarcane had already been introduced.[22] During the Middle Ages sugar was very expensive, and the presence of obesity was observed primarily among the royalty and the wealthy. However, as worldwide production of sugar skyrocketed in the 1800s, sugar started to become less expensive. I found papers linking the rise in sugar intake in the late 1800s with the appearance and rise of diabetes in India. The introduction of sugar to the Native Americans (such as the Pima) in the late 1800s and to the Polynesians in the early 1900s was also

[21] I found this reference by asking questions via Google and Google Scholar. Bhishagranta, K.K.L., *An English Translation of the Sushruta Samhita*. Vol. 1. 1907, Calcutta: Mihir Press.
[22] Blockstein WL. Moses Maimonides; a review of his life and contributions to medicine. Am J Pharm Sci Support Public Health. 1954 Jul;126(7):238-44.

shortly followed by the appearance and rise of obesity and diabetes. Indeed, the rise in sugar intake in the United States in the 1900s also paralleled the rise in sugar intake, and as sugar became cheaper , there has been a transition in which obesity and diabetes is now higher among the poor and disadvantaged. In summary the review of the literature did not suggest that there was a genetic predisposition for diabetes and obesity in the African American or Native American, but rather that it was linked with diet, and not just any foods, but rather sugar.

Thus, one can learn alot from reviewing the literature. But this can take a lot of time. So a natural question is how much can be learned of the past by using artificial intelligence (AI)? The answer is a lot, and I recommend using AI as it may find information you were not aware of. There is some danger using it, however, as AI might also make the mistake of not separating interpretations from facts, especially if it is in the textbooks. In essence, computers tend to be better with providing details and standard viewpoints rather than to present novel ideas, although this is clearly changing. So use AI, but with caution.

Learning on the Battlefield. Doing your homework by reading the literature is critical, but it is only part of the story. When Holmes says, "you see but you do not observe", he was assuming you were at the scene. In the medical field, this commonly comes from seeing patients. As Sir William Osler, the father of modern medicine, said, "He who studies medicine without books sails an uncharted sea, but he who studies medicine without seeing patients does not go to sea at all."

But how does one improve our observation skills? Again, the trick is to ask questions. When you ask questions, it engages you with the patient and leads to better medicine. [Think how awful it is for a patient if the doctor only looks at the computer screen, downloads your history, does a cursory examination, and then initiates a one-way dialogue telling you want you have and what you should do]. When you are curious and ask your patients questions, you will pick up information that may be new and could be helpful in clinical management, but also may provide clues to the cause of their diseases.

The importance of being curious and asking questions has been emphasized by Faith Fitzgerald, a physician from University of California, Davis[23]. Fitzgerald told her story about how she feels everyone has an interesting finding, but you just need to ask the right question, and she challenged her students to find someone who was, frankly, not interesting. The residents accepted

[23] Fitzgerald FT. Curiosity. Ann Intern Med. 1999 Jan 5;130(1):70-2

the challenge and took her to see an old woman that had been evicted from her apartment and was admitted for nutrition and placement. On initial questioning, it did seem the patient had a fairly uninteresting life, working mainly as a hotel maid, and with no unusual illnesses. But when Fitzgerald asked if she had ever been hospitalized, the old lady said yes, she had broken her arm once. That would have ended the conversation for most of us, but Fitzerald asked her how she broke her arm, and she responded that this occurred when a cargo box fell on her. Further questions revealed she was on a steam ship, that it hit an iceberg, and that she was in the hold of the ship with the lower-class passengers when the cargo box fell on her. Because of her injury, she was one of the first passengers put in a lifeboat. And yes, the year was 1912, and yes, she was on the Titanic. There is a wonderful lesson here. Asking questions does not just make the patient feel better, it can be illuminating.

The Power of Anomalies. Anomalies are observations that are not expected, and sometimes counter current thinking. Our natural tendency is to ignore anomalies, or to brush them off as being inconsistent with what we have learned. But they represent a treasure, as they can also represent some of the key evidence that a current hypothesis is wrong. The key to anomalies is to learn as much as you can about them, and try to relate them to both the current thinking as well as to your own ideas. This is especially important as anomalies can also provide key evidence against your hypothesis. As Thomas Huxley said, “There is nothing worse than the slaying of a beautiful hypothesis by an ugly fact”.

Anomalies do not always have to counter an idea, as sometimes they can do the opposite, and end up supporting an idea. An example of this latter possibility happened to me. In particular, there is an epidemic of chronic kidney disease that has been affecting agricultural communities in the hotter regions of the world, and the cause has remained mysterious, with some ascribing the cause of the kidney disease to chemicals and toxins, while others have proposed that it may result from repeated heat stress. Finding the answer is critical, as many of these individuals are poor and in communities where treatments such as dialysis or transplantation is not available, and to date there have been over 60,000 deaths.

As mentioned, a favorite theory has been that the kidney is damaged from the repeated heat stress that the workers undertake when they are in the field. One way to look at this is to evaluate a worker by testing his or her urine before they go into the field and then again at the end of the

day. Our group and others found evidence that at least one in six individuals working in the sugarcane fields was developing some type of kidney injury that could be detected in the late afternoon sample. But whether this was from heat stress or not remained unclear.

One day we only received 8 pairs of morning and afternoon urine samples instead of our usual 20 paired samples. These samples were sent to us in Colorado, so there was a delay of a month or so from when they were actually taken, and the samples came with a note saying that they had trouble getting all 20 samples that day and that we might even consider discarding them since there were too many missing samples. We decided to still look at the samples, and Carlos Roncal[24], one of the leaders in my group, came to me with an interesting observation. Instead of the usual 1 in 6 showing kidney damage, all 8 samples showed massive evidence for kidney injury.[25]

I realized that this was an anomaly, and when I got home that night, I googled to determine if there was anything unusual that date in Nicaragua. In particular, I was wondering if the day the samples were taken may have been an especially hot day. To my excitement, it was the hottest day of the year for that region. I then reached out to some collaborators of mine who were climatologists, and they provided me with a major insight. I had been of the viewpoint that heat stress was important, but the challenge with linking it to climate change was that the mean temperature had only increased by 1 degree Celsius in the last 50 years, and that seemed too minor to explain such a dramatic rise in cases over the last few decades. But what I learned is that while the mean temperature has changed only 1 degree, that the impact of climate change on extreme heat events was much more severe. Indeed, climate change is responsible for nearly 75% of all heat waves today. We thus realized that the problem that day was that a major heat wave occurred, and that the sugarcane workers were not prepared. This is why some left work early, and why those that stayed were at the greatest risk for heat stress and dehydration. And this is why those that stayed all developed kidney damage. Indeed, with further studies we were able to provide very strong evidence that the epidemic was closely linked with both heat stress and climate change, and

[24] Who is also my brother-in-law!

[25] We were looking for crystals of uric acid in the kidney, which can be associated with kidney injury. Al 8 cases had huge amounts of crystals. This can happen with severe dehydration and heat stress.

that it represents one of the first epidemics from global warming today[26]. Importantly, this does not mean that toxins are not also involved.

How to Get New Insights

"Creativity is just connecting things." *Steve Jobs*

Connecting the Dots. As most people know, creativity does not come from thin air, but rather by connecting bits of information into a new idea. Developing that idea comes from broadly reviewing the recent literature about the topic, asking lots of questions, and ideally being at the scene so you can actively observe what is going on. The most important information to connect are the anomalies, and these represent the data that are typically not considered.

One of the best ways to do this is to think when you are relaxed, not when you are at work. Begin by asking a question, and if you have a few questions that interest you, pick the most important one. Then, daydream about it. Relaxation helps open the mind and remove tension. Sometimes one can get this by running (getting an endorphin high), or by walking in the woods. Taking some time to blank the mind, such as by meditation or focusing on some aspect of nature (flowers, animals) for a few minutes can be helpful. A drink of alcohol or a small amount of chocolate or sugar can also remove inhibitions. And for me the best way is to go to bed thinking about the question. I find that I seem to continue to work on it while I am asleep, and quite often will wake up with some type of insight. In the past I used to keep paper and pen near my bed, although over time this has become so common that I no longer need to do this. And do not worry if you do not get an answer right away. Just the process of thinking about a question, even if it is wrong, is better than not thinking at all.

Ideas in the Absence of Observation. We have talked about how the majority of discoveries are triggered by an observation that the individual tends not to forget. In this case, the observation may trigger an insight that can lead to the discovery of the cause, or it can generate the question that will continue to bother the individual to the point that they will study that condition for years until they get the critical insight they need to solve the question.

[26] Glaser J, Lemery J, et al. Climate Change and the Emergent Epidemic of CKD from Heat Stress in Rural Communities: The Case for Heat Stress Nephropathy. Clin J Am Soc Nephrol. 2016 Aug 8;11(8):1472-1483.

Hmm, I wasn't expecting so much imagination today.

There are occasions in which one generates an insight in the absence of a specific observation, which can be viewed as a *conceptual innovation*. This is especially true in physics. Indeed, many of the great breakthroughs in physics involved conceptual innovation, such as the existence of black matter and black energy. Nevertheless, in many cases these discoveries are based on previous scientific observations. Furthermore, there often is some type of random observation that triggers the insight, such the apple falling on Newton that initiated him to ponder the laws of gravity[27]. Einstein was puzzled about how the observation that the speed of light is constant might affect velocity and time. He is said to have gotten his idea of general relativity by looking at a clock and imagining what it would be like if he were on a train moving towards the clock near the speed of light. While on the train, time would appear normal, relative to those not on the train, but the time would have to shorten if the speed of light were indeed constant. Thus, if one could travel in a spaceship near the speed of light, and then come back to earth, one would be much younger in appearance to everyone else. You might think that is a solution to aging! However, if you were on the spaceship, you might appear to look younger to those on earth, but from your standpoint, you are the one aging normally and the people on earth are aging in an accelerated manner. So it is not the cure of aging, but rather the opposite. Too bad!

Stimulating the imagination can be very helpful. If you have trouble, follow this crazy idea. My father liked to say, "If frogs had wings, they would not bump their asses so much." It sounds crazy, and it is. But just try imagining frogs flying around with wings. If you are with me, you are either crazy or on your way to be a discoverer. Or both!

Simplifying the Idea. Sometimes there is so much information that it seems impossible to make sense of the data. This often leads to us categorizing things, such as the Dewey Decimal Classification system that is used in libraries to group books on various topics. While this classification is outwardly helpful, sometimes these types of categorizations can actually work against us, as they force us to think a certain way.

It is thus important to 'decategorize' your findings, and to free them to their simplest level. One way to do this is to distill the major findings to a few critical points. This may make it easier to connect the dots and make a new insight. Simplifying things may allow the underlying

[27] There is controversy over whether this really happened.

discovery to be easier to see. The danger, of course, is determining what key things one needs to focus on, for when one simplifies things, one may remove some of the critical information.

Another useful approach is to think how your idea relates to nature and evolution. Evolution is an experiment that has continued for millions of years, and nature knows a lot more than we do. Often discoveries are related in some way to nature's own experiments.

Steal like an Artist. Austin Kleon wrote ***Steal Like an Artist***, in which he says that new ideas spring from old ideas, and that the way you can become a great artist is to first mimic the artist you like, and then over time branch out to create your own style. There are certainly lots of people with ideas that challenge the establishment, and it is absolutely fine to adapt their ideas, and then further develop and extend their concepts into one that you champion. I believe it is important, however, to credit individuals that you have learned from.

Developing a Big Picture. Another thing that is common in people who do research is the process of diving deeper and deeper into a subject, and this often tends to progressively narrow the scope of our work. It may appear like we are drilling a hole, and as we gain more and more expertise, our topic gets smaller and smaller, until it is a tiny but beautiful diamond at the bottom of the hole. Sometimes this information can lead to major breakthroughs. However, often it seems of less relevance to the world. One way you can counter this process is to try to place the context of your finding in a bigger picture. I call this creating an aerial view, for instead of going down the hole, you go up a tree and look out across the fields to the horizon. This is best done by trying to relate your finding to fields of biology and science, or even to wider fields like history, geology, and chemistry—sometimes referred to as planetary biology-based approach.[28] The idea is to continue to read and ask questions that can allow you to connect your tiny diamond with the rest of the world.

Collaboration and Competition

[28] Steven Benner, a leader in the science trying to identify the origins of life, has called this "planetary biology". Benner SA, et al. Planetary biology--paleontological, geological, and molecular histories of life. Science. 2002 May 3;296(5569):864-8.

"Don't worry about people stealing your ideas. If your ideas are any good, you'll have to ram them down people's throats." *Howard Aiken, Physicist and Early Computer Geek*

Collaborating with the Experts. In general, collaboration should be encouraged, especially when you are outside your field. If you find yourself as an amateur trying to teach the experts that they might be wrong, you might benefit by first persuading an expert to join you. That individual will not simply add weight to your argument, but is likely to know some additional information that might help bolster your argument, or for which you should address. So asking an expert to join you is not a defeat, it is something highly desired. What is more, sometimes it is the expert who solves the critical question that you originally brought to the table.

A great example is the story of the Alvarez father-son team that figured out why the dinosaurs went extinct.[29] Walter Alvarez was a geologist who was interested in the transition from the Cretaceous Period (when dinosaurs still roamed the earth) and the Tertiary Period (the period immediately after when mammals took over). Geologically, these periods could be separated by looking at layers of rocks, as the end of the Cretaceous was associated with a layer of clay, while the Tertiary the layer was more of coal, and there was a fine light yellow-gray line that separated the two. Walter realized that this layer reflected the time in history when the dinosaurs went extinct, and he wondered how long that might have taken. He decided to ask his father, Luis Alvarez, who had already won a Nobel Prize in Physics. Luis knew that there was an element, iridium, which is from outer space, but deposits at a slow steady rate on the earth, and so he suggested that measuring the iridium in the layer might allow a calculation for how long this transition period may have lasted. But when the levels came back astronomically high (sorry for the pun), it meant that the world had been hit by a large iridium-containing object from outer space, such as an asteroid. They realized that the asteroid would have spewed dust and dirt in the air that could darken the skies for decades, dropping temperatures and resulting in a mass extinction. About 10 years later the crater of that asteroid was found in the Gulf of Mexico just north of Yucatan. Luis then had the pleasure of not only getting a second Nobel Prize, but also sharing that with his son.

[29] Alvarez LW, Alvarez W, Asaro F, Michel HV. Extraterrestrial cause for the cretaceous-tertiary extinction. Science 1980; 208:1095-108

Being friendly pays. It seems like there is always someone who is doing something similar to you, and while it may ideally lead to collaboration, sometimes it turns into a competition. The first rule in competition is to be friendly. There can be unexpected benefits. One time I was at a meeting in which I developed a new method to inject substances into the kidneys of laboratory rats, and I was using this to test some ideas I had on how kidney damage might occur. My main competitor came up to me and asked me if I could explain to him how to do this in more detail. So I showed him everything, including the little tricks that made the procedure easy and reliable. One of the people in my group overheard me. "Why would you tell him everything? Now he will almost certainly beat you." I went back to Seattle quite dejected and told my mentor, Dr William Couser, what had happened. "Rick, I would not worry. Given that you have almost completed your studies, the chance that he will publish before you is remote. But the chance that you may have made a friend is high." Later I learned that my competitor became a staunch supporter of my work, including when he was reviewing my papers and grants.

Naughty Collaborators. There are occasional times when a collaborator or mentor can fail you. For example, in the first chapter I mentioned how Vogl's mentor actually published on the discovery of the first diuretic without including Vogl's name despite Vogl being the discoverer. Another sad example relates to Albert Schatz, who was a graduate student in the laboratory of Dr Selman Waksman at Rutgers University. Schatz was taken by Fleming's discovery of penicillin and that it came from a mold. However, there were lots of infections that penicillin was useless against, including tuberculosis. Schatz became obsessed with finding new antibiotics, and he would spend time collecting soils, including from swamps, to see if he could identify a new treatment. Finally, using soils collected from a manure field and another from the throat of a chicken, he was able to grow a fungus that produced a substance that could inhibit the growth of tuberculosis. The discovery was so significant that a patent was submitted by Waksman and Schatz. Soon the pharmaceutical company, Merck, was working with the team, and by 1947 the first antibiotic for tuberculosis, streptomycin, went to market. Indeed, it was given to my father, who had been stricken by tuberculosis and had been placed in a sanatorium near Fond du Lac, Wisconsin. Then came the bad event, in which Waksman negotiated to have all of the royalties assigned to himself. He also failed to disclose this to the public or to Schatz. Eventually it went to

court, and Schatz ended up receiving some of the royalties, as others did from Waksman's laboratory. Sadly, the Nobel Prize of 1952 went to Waksman, and Schatz was left out.

Yet another story relates to the discovery of DNA. In the early 1950s, there was competition between major laboratories at three Universities (King's College in London, Cambridge University, and California Institute of Technology in Pasadena) as to who would be the first to identify its specific chemical structure. One of the special methods that was being used to visualize DNA was X-ray diffraction, in which X-ray beams are passed through crystalline DNA and the way the beams are diffracted can be used to elucidate the structure. One of the best at doing this was Rosalind Franklin, who had learned the technique in Paris, and had joined the laboratory of Maurice Wilkins and Raymond Gosling at King's College. Indeed, by late 1951 she had evidence that the DNA existed as a helix, which she presented at a seminar in which a young research fellow from Cambridge named James Watson was present. Watson went back to Cambridge and developed a model of DNA suggesting it was a triple helix, and presented it to Franklin, but she was unimpressed with the argument. Then, in early 1952, Franklin was able to get better resolution and had good evidence that the DNA was in fact a double helix. By January 1953 she was again visited by Watson, who brought with him a manuscript that had been submitted by Linus Pauling from UC Berkeley that also suggested that the DNA was a triple helix. He then asked Franklin to collaborate with Francis Crick and himself so they could together beat Pauling, and he told Franklin that they could help interpret Franklin's data, for which Franklin became angry. Watson then met privately with Wilkins and during that discussion, Wilkins showed Watson the X-ray image generated by Franklin that demonstrated the DNA structure was actually a double helix. Unfortunately, he did this without her permission.

Watson then returned to Cambridge where he and Crick pondered how the DNA structure might fit together as a double helix. Then, on February 28th, while at lunch at the Eagle Pub, the two realized not only how the two double helix strands might combine with each other, but also how this allowed them to separate and then duplicate. Crick rapidly prepared and submitted a paper to Nature that was published in April 1953, describing DNA as a double helix, with specific pairing of the bases and where the strands of the helix were parallel but ran in opposite directions. Franklin had also put together a similar manuscript but had still not submitted it at the time of the publication.

So what went on here and what should have happened? It seems that both the team of Watson and Crick and that of Franklin and her collaborators should have been credited with key aspects of the discovery. However, Rosalind was not very friendly, and while she could be charming outside the laboratory, when it came to research, she tended to be standoffish, argumentative and relatively unapproachable, and when Watson proposed a collaboration, she refused. Nevertheless, it is my opinion that Watson and Crick should have shared their manuscript with Franklin before submitting it, and also should have asked her to be a coauthor and contributor (and ideally including the famed image in the paper).

The bottom line is always be friendly and maintain your integrity. Mark Twain wrote, "Do the right thing—it will gratify some people and astonish the rest." If a mentor or collaborator is naughty, see if you can work it out with them first. If things fail, attack!! We will talk more about the tactic of fighting in a later chapter.

Chapter 8 Prove the Discovery is Real

"However beautiful the strategy, you should occasionally look at the results." *Winston Churchill*

My mentor, Bill Couser, looked up after reading my research proposal, and said, "You're jumping again. You are skipping key steps in proving your hypothesis. Instead of going from A to B to C to D, you are jumping from A to D, then G. But your idea is good, you just need to tighten up how to go about proving it."

I was learning the hard way that the process of coming up with an idea is often quite different from the process of proving that it is right. Ideas were easy for me, as I seemed to be a professional dot connector, but proof required a linear type of thinking. For some reason I am good with the former—even Couser kept a folder in one of the drawers of his desk labeled Johnson's crazy ideas, and my friend and collaborator Stuart Shankland would keep a tape recorder in his office that he would turn on when we would brainstorm. Not even I knew what I was going to say, but, at least occasionally, it was good. I do not want to brag, though, as my father would say, "even blind hogs root up truffles once in a while."

But it is often said that ideas come from inductive thinking, while proof comes from deductive reasoning. The basic idea is that to prove things, you need to do a stepwise, logical series of tests, known as the *scientific method*, or perhaps run a very well-designed *clinical trial*. Sometimes you can also prove by *anecdote*, especially if the outcome is spectacular, although it is considered less strong than the other methods. Regardless, each of the methods have their own weaknesses and rarely is proof absolute.

So it may be important to 'change up' your approach when you switch from idea making to idea testing. Nevertheless, there is hope for daydreamers like me, for research is often teamwork, and you can make sure you have a person on your team who is a great "linear' thinker. For me, I was benefitted early in my career to work with people who were really good at their A,B,C's and

could keep me on track.[30] And of course, the more you do this, the better you get, so that over time you can recite the alphabet according to Webster just as well as the others.

'Thought' Experiments

When it comes to generating evidence to support a hypothesis, there is one type of experiment you can do from your sofa, and these are "thought experiments". It is practically a game, which I affectionately call "Is there evidence?" The idea is to open up google, bing, ChatGPT, or some type of computer search program, and to make a prediction based on your hypothesis, and then to see if someone has already done this. If they did, this becomes evidence you can cite when you publish your hypothesis, and if not, you can include this as a prediction and hope someone else (or possibly you) will confirm that prediction in the future. If there is an opposite result, you can also modify your idea.

This approach is not good for proving experiments, as the world tends to want to see the proof done by the scientific method and direct experimentation. But they are an excellent way to develop and extend your hypothesis. Thought experiments also have the weakness that we tend to look for evidence supporting our idea rather than the opposite (more on this later).

Thought experiments are great if you are a dreamer, as you do not have to be that observant, or even that logical. So go ahead and sit down, daydream and do your own google experiment. Indeed, when I was a kid, I always tried to find a seat in the back of the room and close to the window so I could daydream. Daydreaming was a great way to relax the mind, but sometimes it would backfire. Once, when I was a freshman at the University of Wisconsin, I was daydreaming in the back of my physics class. I awoke when I felt a tap on my shoulder, and I looked up to see the Professor standing before me. He seemed upset, and many of the students stared at me with worried looks.

[30] It is often best if a person in your laboratory is great at this. I am forever indebted to my right hands, Kathy Gordon and Pam Pritzl, who were my research technicians and always kept me on track. I also am especially appreciative of Wei Mu, who is both an inductive and deductive scientist who kept challenging our work and helped make it appear fool-proof. (Remember, there is no science that is truly fool-proof).

Quiet, please, he is in a thought experiment, and it is not going well.

"Richard, you may have not been listening, but I asked you to answer the third question of today's assignment." There was stone silence as he looked around at all of the students.

I was in trouble, and what was worse, I could not recall what chapter we were reviewing. "I apologize, sir, for being distracted. But can you remind me what chapter we are on?" I quickly pulled the textbook out of my pack.

My response tweaked the Professor, and he replied, "Richard, what chapter would *you* like to be on?" I squirmed and at the same time noted that some of my classmates were snickering.

I decided to make it as easy as possible, so I quickly said, "Chapter 1, of course." He responded, "Okay, then, Chapter 1." I opened the book to the page where the questions were and, thankfully, answered the question correctly. The Professor smiled at me, and I knew I was not dead, but had been given a not-so-subtle warning not to daydream in his class again!

I am not quite sure why I am telling you this story, but I think the key message is that daydreaming can be a great way to come up with new ideas, but just don't daydream in your physics class. If you do, though, don't dream of castles and dragons, but rather dream of black holes, dark energy and supernova. And if that is what you are really doing, tell your professor if he wakes you up, and you might just get extra credit.

The First Clinical Trial: Finding a Cure for the Great Sea Plague

Today clinical trials are how we learn if a drug works, and so it may seem crazy to know that it was not long ago when the first clinical trial was performed. The hero was a 31-year old surgeon who tackled a disease that was the curse for those who spent months at sea.

The great sea plague was a wretched disease, a mariner's nightmare, worse than war, and for which there was no cure except to get to land. The disease had been known since the Great Crusades, but it came to its height beginning with the Age of Discovery, when mariners sailed for weeks or months to find new trading routes and to explore distant shores. Adventurers such as Vasco de Gama and Sir Francis Drake all lost sailors to this woeful disease, but no voyage suffered more than that led by Commodore George Anson.

It all started when a British ship was stopped by Spaniards, and the British captain named Jenkins had his ear cut off and sent to the King. England declared war, which became affectionately known as the War of Jenkin's Ear. Commodore George Anson was given the charge of sailing to the west coast of South America where he was to harass Spanish ships, encourage the Peruvian natives to revolt, and to capture the Manila galleon, a Spanish treasure ship that took gold yearly from Acapulco back to the Philippines and eventually Spain. Commodore Anson assembled a fleet of 8 ships with over 2000 sailors, soldiers, cooks, and servants. On September 18th, 1740, the ship set sail, leaving the Isle of Wight for the Madeira Islands and then across the Atlantic for South America. Life on the ships was difficult, as they were overcrowded and hygiene was poor. Early on a febrile illness with diarrhea swept through the crew, and while it was transient, many sailors were left weakened. Food consisted primarily of biscuits, butter, cheese, salted pork or beef, and beer or brandy. A sailor on one of the ships, the *Tryal*, wrote that bread was toasted over burning brandy to kill the maggots. Nevertheless, all but one ship reached St Catherine's Island off the coast of South America, with the other turning back only to be captured by the Spanish. However, the island offered few supplies except fresh beef. After a brief stop, the ships sailed into the Strait of Lamaire that began the journey around the Cape of Good Hope. It was the worst time of year for taking on this task, and for the next few months the sailors had to battle gale winds, sleet and snow.

The illness began while they were rounding the Cape. The first case occurred on March 7th. Sailors would complain of feeling tired and weak, with aching joints and a loss of energy, causing them to lie huddled on the deck. The mouth became sore, and the gums would bleed and ache, causing eating to be painful. Infections of the gums would make the teeth wobble and fall out, and the gums would overgrow those few teeth remaining, at times extending like loose strands. The bleeding and infections caused a horrid stench to the mouth. The skin became thickened and discolored with bruises, and bleeding could occur in the joints. The body began to waste away, and depression would set in and overtake the spirit. Some sailors became anxious, delirious, become hysterical, or even have a seizure with the slightest provocation. Sometimes individuals were so frail that they could drop dead with the sound of a cannon shot. It was a wretched illness, and hundreds died. Only four of the seven ships successfully rounded the Cape where they were able to find food and shelter on the island of Juan Fernandez.

Here, on the island of Robinson Crusoe fame, the sailors were able to recover, eventually allowing Commander Anson to continue their epic journey to the coast of Peru, where they indeed captured a few Spanish ships. They then sailed across the Pacific only to see his sailors develop scurvy once more, with additional deaths. But success was to be Anson's legacy, for he did capture the Manila galleon in the Philippines, eventually returning to England in 1744 with a treasure worth 480,000 British pounds. Anson's return was met with great celebrations and Anson was eventually given the title of the first Lord of the Admiralty of the Royal Navy. Unfortunately, only 146 of the original 1955 sailors survived the three- and a-half year trip around the world, with nearly 1300 men having died from the dreaded scurvy.

It was at this very time that a young man named James Lind had been hired as a ship's physician for the HMS Salisbury, a 50-gun, 960-ton ship of the Royal Navy that patrolled the English Channel. Lind was a Scotsman who had received his medical degree from the College of Surgeons in Edinburgh, graduating in 1739 when he was only 23 years old. His desire had been to go to sea, and his first position was on the HMS Salisbury. He had always had an interest in scurvy, and had been taught in medical school that it was a rotting disease that might be best treated by acids. His moment for testing his idea came in May 1747, after his ship had been to sea in the English Channel for several months. Over a period of only a few days, he watched as nearly 80 of the 350 crew fell sick. The illness swept through the crew, causing them to become progressively weak, with bruises and spots on their legs, bleeding mouths, putrid gums, horrid breath, and aching joints. The sailors were placed in the sick bay, which was a crowded hold in the ship where they huddled together and were fed a sugary gruel as solid food was difficult to eat. The cure was to get back to land, but it would take nearly four weeks before they could reach the port in Plymouth.

Then Lind got the idea that he might try various possible treatments on the crew to see if one of them might work. He identified 12 individuals who were suffering from scurvy and separated them into groups of two. Two individuals were given the treatment he had learned in medical school, consisting of a spoonful (25 drops) of sulfuric acid that they had to gargle three times a day to clean their mouths. Two others received nutmeg mixed with garlic, mustard seed, horseradish, balsam of Peru and gum myrrh that was mixed with cream of tartar and barley water and drunk three times a day, following the recommendations of an old hospital surgeon. Two

received two spoonfuls of vinegar three times a day to clean their mouths and gargle or add to their gruel. Two were given a quart of cider. An additional two sailors received two oranges and one lemon each day. Finally, two of the sicker ones who had their legs tightened in spasm were given a half pint of seawater to drink each day.

At the end of six days, there was a remarkable recovery by the two sailors who had ingested the oranges and lemons, and a partial recovery by the two who drank the cider, whereas all of the other sailors showed no improvement or worsening of their condition. And so it was that Lind discovered that scurvy could be treated by citrus fruits. He eventually published his findings in 1754, but it was not until the 1790s that the British Navy required that sailors be provided lemon or limes when at sea.

The Birth of the Scientific Method: A Country Physician Identifies the Major Killer of the 19th Century

Tuberculosis, also known as the Great Consumption, devastated Europe and much of the world in the 19th century. Over the past centuries many famous people died from the disease, including Robert Louis Stevenson and John Keats. Known as "the captain of the men of death" it would cause people to slowly wither away. Fevers were often high and uncontrolled, causing the individual to awaken at night in drenching sweats, and weight would fall dramatically over months. The skin would take on a dusky pallor, and the individual would become progressively anemic, weak and feeble. The key sign was the coughing up of blood and blood clots, which could occasionally be dramatic. Frederick Chopin, for example, would occasionally cough up blood during his performances.

The cause of the disease was unknown. For years suspicions ruled that it might be an affliction passed by vampires or evil spirits. However, a turning point occurred in 1869 when a French doctor, Jean-Antoine Villemin, discovered that tuberculosis was infectious, as he was able to pass the infection to rabbits by injecting them with ground-up tissues taken from human victims. Most of the world ignored this important observation. Not everyone, however.

Robert Koch was the son of a miner born in 1843 in a small town in north Central Germany in the Harz Mountains. As a young man he had wanted to be a naturalist, and to travel throughout the world categorizing everything from mosses to birds, much like Darwin had done on his round-the-world tour on the *Beagle*. His love of travel was so great that at one point he almost took an offer to travel to America to assist a shoe merchant. However, he decided to attend medical school in Göttingen University, where he was introduced to an emerging idea that infections might be passed by small living organisms called bacteria. Following graduation, Koch served in the Franco-Prussian war and then moved to Poland in 1872 where he worked as a family physician.

Because of his interest in bacteria and their potential role in infections, his wife gave him a microscope as a birthday gift when he moved to Poland. He would work as a physician, but when he had free time, he would do research, even at night. He was particularly interested in the disease anthrax. Anthrax was a wicked disease that would kill cattle, usually by causing internal bleeding, but it could also infect people, especially those who handled the carcasses. People who became infected could develop painful skin infections characterized by ulcers and black lesions, and rarely as pneumonia (which was often fatal). There were prior reports that bacteria could be identified in the spleen and other organs of animals dying from anthrax, and Koch began his studies by confirming these findings using his microscope. But then he got the idea, that if these organisms might be the cause of anthrax, then he could prove it by passing the bacteria to another animal and see if it also developed disease. To address this question, he caught wild mice in his barn. He then took a wood sliver and stabbed the spleen of a cow that had died from anthrax and used it to puncture the skin of the mice. After a few days, the mice developed anthrax! He then tried to grow the bacteria from the mice. While it was initially difficult, he eventually succeeded in growing the bacteria by culturing the bacteria on a plate that contained the inside of an ox's eye that had gelatin-like material. He then injected those bacteria he had grown back into normal mice, and they also developed anthrax. He now had enough evidence to argue that the bacteria were indeed the cause of anthrax, and he published his work in, of all things, a friend's botanical journal in 1876.

He soon became known for his outstanding work, and in 1880 he was invited to Berlin where he worked at the Imperial Health Bureau. After meeting with Pasteur, he decided to try to find the cause of tuberculosis. First it took him a while to figure out how to stain the bacteria. There was a little bit of serendipity, for he found that the bacteria stained with an old bottle of

methylene blue, but not a fresh bottle of it, and it was because the old bottle had slowly become more alkaline over time. So he ended up adding potash to new methylene blue which allowed him to stain the bacteria. Eventually, he also found a way to grow the bacteria using human coagulated blood as the culture fluid. After this preparation, he decided to do similar experiments as he had done with the anthrax. After just 6 months, he had been able to take infected sputum from a person, infect guinea pigs, then grow the bacteria from the guinea pig, and then inject other guinea pigs. When he completed his experiments, he had not only identified the bacteria that caused tuberculosis, but found that he could both grow it and infect other animals with it.

On March 24th, 1882, he presented his findings to the Berlin Physiological Society. In the audience were many famous physicians, including Friedrich Loeffler, Hermann von Helmholtz, and Paul Ehrlich. Notably absent was Rudolf Virchow, a famous physician and pathologist, but an ardent disbeliever that germs such as bacteria could cause disease, and also a disbeliever of evolution. Koch, who was just 38 years old, brought with him his microscope, with tissue samples, stained slides showing the bacteria, and even cultures in test tubes. He then began his talk by discussing how tuberculosis was the greatest killer of the 19th century, and that one in seven people die from tuberculosis. He presented his research, showing that he could identify the tuberculosis bacteria, grow it in culture, infect animals with the bacteria, and then grow the bacteria from the infected animals and infect new ones with it. It is said that Koch, who had trained as a family physician and was only 38-years old, was initially soft spoken and shy, but as the lecture proceeded and the evidence that he had found the cause became more apparent, the he ended up speaking with complete confidence. At the end of the talk, all of the audience were silent, as if in awe, and there were no questions. Slowly, members of the audience walked up to the table to look through the microscope themselves at the bacteria that was the cause of the greatest killer of that time. Within days the world knew of the results, and the overall response was dramatic. There were some individuals who were not convinced, such as Virchow, but he was from the old school and was unlikely to ever change his mind.

Around 1890, Koch made an announcement that he had found a potential cure of tuberculosis. Specifically, he had made a filtrate of the fluid that the tuberculosis bacteria were being cultured in, and found a protein that he called tuberculin. According to Koch, when he gave tuberculin to guinea pigs, he could prevent the animals from getting tuberculosis. The world again

responded with the greatest excitement, and many physicians went to Berlin to confirm the findings. One of them was Sir Arthur Conan Doyle, who, as you know, authored the Sherlock Holmes series. So, I think we can consider Holmes as being present. And, unfortunately for Robert Koch, it turned out that the tuberculin protein could not prevent infection, and the world would have to wait for another 57 years before the first antibiotic for tuberculosis was discovered by Schatz and Waksman. Nevertheless, the tuberculin protein ended up being key for confirming if someone has had exposure to tuberculosis.

Koch became famous for his series of experiments to prove that tuberculosis was caused by bacteria. The ability to identify a bacteria from an infected person, to then isolate and culture it, and to pass it to a laboratory animal and show that they get disease became known as Koch's postulates and became central to what is called the Scientific Method. Today the use of Koch's postulates has been extended to disease processes and risk factors in general, and usually involves documenting that the risk factor is associated with the disease (epidemiological evidence), that it can cause the disease in animals (laboratory evidence), and that preventing or treating the risk factor can block the disease in humans.

Extremist Approaches: At the Heart of it All

"There is only one difference between a madman and me. The madman thinks he is sane. I know I am mad." *Salvador Dali*

Discoveries are best proven by the scientific method or by clinical trial. However, often the discoverer is passionate about his or her discovery but frustrated that the establishment pushes back, and this conflict between intense desire and intense rejection can lead to extremist measures. Recall how Barry Marshall became progressively frustrated that so many scientists either ignored or rejected his ideas, and how this led him to swallow the bacterial cultures to prove that it could cause peptic ulcer disease. I would not have wanted to be in his house that night that he told his wife what he had done. However, all turned out well, for not only was he able to prove that the infection could cause gastritis, it also resolved spontaneously. For his discovery he received the

Nobel Prize, which is not too bad! And we are left with the realization that anecdotal evidence can be convincing, depending on how it is done.

However, the consequences of 'Kamikaze Medicine", as this approach has been called, is not always rosy. A sad example is the story of Daniel Carrion (1857-1885), who was the son of a miner (like Robert Koch) and from Cerro de Pasco, Peru (where we did our studies on cobalt). Carrion moved to Lima where he became a medical student and worked at the Dos de Mayo hospital. He witnessed an epidemic of some type of febrile illness that occurred in 1882 in which thousands of workers died during the construction of a railroad between the port of Callao and La Oroya, a city in the Andes. The infection became known as Oroyo fever and was characterized by high fevers, joint pains, and severe anemia. Carrion noted that there seemed to be an association of Oroyo fever with a chronic warty skin condition known as verruga peruana (Peruvian warts), as both conditions often frequented the same family, and also because some patients with Oroyo fever would later develop verruga peruana. The more he thought about this association, the more he became convinced that they might represent the same disease, but that they manifested differently based on timing and other factors. He then got the idea that he might prove that they are the same disease by injecting himself with some of the drainage from the skin lesions of a patient with verruga peruana to see if it would cause Orroyo fever. Clearly he needed to talk to someone sane at this point, as this is not a wise experiment. Nevertheless, he proceeded by scraping some of the warty and blistering lesions from a 14-year old boy, then grounding it up with a pestle and mortar, followed by injection of the cruddy mix into each arm (with the help of friends). Like a scientist, he then recorded his condition daily. Sure enough, after about two to three weeks, he started developing fever. His condition continued to deteriorate with each subsequent day, and eventually he developed all of the manifestations of Oroyo fever, including the severe anemia. He eventually became delirious and died about 5 weeks after he had injected himself.[31] Later Oroyo fever was shown to be due to a bacteria (*Bartonella*) that is passed by the bite of the sand fly. Today the condition is called "Carrion's disease" or bartonellosis.

[31] A famous saying among medical researchers is "publish or perish" to emphasize that it is important to stay productive in a field where survival is so commonly based on grants and productivity. One of my friends, who heard this story, suggested that Carrion must have mistakenly heard the phrase as "publish and perish". I admit this is sick (and likely inappropriate) humor! That is why it is hidden in this footnote.

Another example relates to the antics of "Wild" Bill Harrington (1923-1992) who was at Washington University in St Louis. In the late 1940s Harrington was profoundly affected when he took care of a teenage girl who had developed a severe bleeding disorder in which she had almost no platelets in her blood. Just as we have red blood cells (that carry the oxygen) and white blood cells (that fight infection), we also have platelets in our blood that help make clots in the event there is bleeding. However, rarely people can suddenly lose their platelets and then can be at risk for bleeding. When this happens, little red dots form on the skin and on the roof of the mouth, and occasionally severe bleeding may occur. In fact, when I was a medical resident I received a phone call from my younger brother who described these findings to me, and I was able to direct him to the closest emergency room where he was diagnosed with this condition, which is known as ITP.[32] In the case of the girl, it was especially bad as the bleeding was from the vagina and she was accused of having a miscarriage when in fact she was not and had never been pregnant.

Harrington never forgot the patient, and over the years he saw additional cases. He became passionate about what might be the reason these patients had low platelet counts, and he speculated perhaps there was some factor in their blood that might be removing or destroying their platelets. So he decided to inject the plasma from patients with ITP into himself to see if it would cause a fall in platelets. Some of the people in his laboratory also volunteered, and he also got several people with cancer to agree to being injected.[33] The findings were dramatic. After receiving the plasma, Harrington and his volunteers began developing signs and symptoms of ITP, especially a drop in their platelet count and the appearance of red dots all over their body. Harrington was the sickest, however, and developed some delirium and bleeding from his gut that required his admission to the intensive care unit. Fortunately, Harrington and his volunteers recovered over the next several days. Later it was shown that ITP is an "autoimmune" disease in which antibodies are produced against the individual's own platelets. Today the disease remains dangerous due to the risk for bleeding, but treatments to suppress the production of antibodies are very effective.

Harrington was clearly lucky, and his research approach is not recommended. It was studies like his and that of Carrion that led to a requirement to have an impartial committee (the

[32] Idiopathic thrombocytopenic purpura, a complicated name we doctors like to show we use to show that we know what is going on. It means our platelets are gone, we have bruises all over, and we do not know the cause.
[33] I doubt if this involved informed consent.

Human Subjects Review Committees) review and approve research before it is allowed to be performed. Nevertheless, it is both interesting and outrageous to hear about these extremist approaches. However, my favorite story, and one that tends to be crazier than it is dangerous, concerns a gentleman named Werner Forssman, who I believe wins the award for obsession in research.

Let us go back to Berlin in the late 1920s. Werner Forssmann, a young man of Prussian descent, received an outstanding education in one of Berlin's best schools (the Askanische Gymnasium), where he had studied history, theology and literature, followed by medical school at Friedrich-Wilhelm (Humboldt) University, another top program, graduating in 1928 at the age of 24. Following graduation he moved to Eberswalde, a town near Berlin, where he started an internship in surgery at the Auguste-Viktoria Hospital.

As Forssmann started his surgical residency, he was struck that current practices to evaluate the heart such as listening to the heart sounds, obtaining X-rays, and even performing an electrocardiogram could not always tell what was going on in the heart itself. He then recalled that, as a medical student, he had read papers by the French physiologist Claude Bernard, who had succeeded in placing catheters into the hearts of dogs where they could directly measure the pressures and flows. This gave him the idea that perhaps a catheter could be placed into the human heart of a living person. Not only could pressures be measured, but it might also allow the direct injection of medications that could help treat heart disease.

He became consumed by the idea, and he went to the anatomy laboratory and examined a cadaver. Whereas the veins in the arm can consist of complex branchings and criss-crossings, there was a larger vein on the inside of the arm that appeared to have a direct path to the heart. Cutting down to the vein, Forssmann inserted a vulcanized rubber tube that was normally used to drain the bladder, and he watched with great happiness as he could advance it up the arm, into the chest, and into the heart. Delighted with his finding, he approached the head of surgery, Dr. Richard Schneider, and suggested that it should be possible to insert a catheter into the heart of a living person. Schneider liked the idea, but was worried that it might cause an irritation to the heart, causing it to fibrillate (i.e. stop beating). So Schneider told Forssmann that he must first try to do this in some animal, such as the rabbit or dog.

Forssmann, however, did not want to listen to his Chairman, as he viewed the procedure as safe. His inquisitive and rebellious nature could not be controlled, and he became obsessed with proving that this procedure could be done. In later years he admitted that if he had actually done experiments in rabbits as suggested, that he would have never proceeded further, as the rabbit is extremely sensitive and often has a temporary cardiac arrest when a catheter is placed into its heart. But Forssmann did not know this then, and so secretly he planned to do this procedure on himself.

It was a summer night in 1929. Forssmann persuaded another medical student, Peter Romeis, to be his assistant. They sneaked into the operating room, and with the help of Romeis, cut open Forssmann's skin at the elbow, where they dissected down to a large vein. Romeis then helped Forssman insert a vulcanized rubber bladder catheter and advance it about one foot. Romeis then became very nervous and quarreled with Forsmann, and eventually Forsmann agreed to stop the procedure. However, a week later, the obsessed Forssmann was back, this time without Romeis. Instead, he asked a nurse, Gerda Ditzen, to help him. She worked in the operating room and would provide the surgical tools and aid with the cutdown to the vein. She actually offered to have the procedure done on her, but Forssmann wanted to do the procedure on himself to ensure it was safe. He then cut down to his own vein, and using the vulcanized rubber catheter advanced it a little more than two feet (65 centimeters).

With the catheter dangling from his arm, he walked two floors down to the basement X-ray suite. Here he asked another nurse to help him. Standing in front of an X-ray (fluoroscope) machine, he would move the catheter back and forth so he could better see its shadow on the x-ray image, which he could see only because the nurse would hold a mirror behind the machine. As he was evaluating if the catheter tip was in his heart, his friend Peter Romeis showed up and tried persuade Forssman to stop. However, Forssmann would not change his mind and continued. During the procedure he felt a sense of warmth, and sometimes would cough as he moved the catheter, but he was able to confirm the tip was in his heart..

Within one hour after finishing the procedure, the news had spread throughout the hospital, and the following morning Forssmann was called to Dr Schneider who reprimanded him for his actions. Forssmann responded that the procedure could be of great importance and that he wanted to publish his findings. Schneider, who liked Forssmann, agreed but argued the procedure should

not be done again in any healthy person. However, if there was someone who was dying with no hope for survival given current treatments, that it might be tried as a means for delivering medicines directly to the heart.

At that time, there was a young woman who was dying of a severe bacterial infection following childbirth. It was still 3 years before Gerhard Domagk would discover the first effective antibiotic for this condition, and the patient had very low blood pressure and was dying. Forssmann inserted a urinary catheter into her vein and successfully placed it in her heart, and then they injected various medications to try to make the heart work better (consisting of a digitalis extract and an adrenaline compound). While it did not prolong life, it did show the feasibility of the approach, and Forssmann submitted his paper which was promptly accepted for publication at the end of the year.

However, Forssman had gotten a reputation of being rebellious, impulsive, and crazy, and Schneider realized that it was best for Forssmann to change his residency, and helped him get a surgical residency position at the Charité Hospital in Berlin. He started his residency in October, but a great uproar occurred when his paper was published in November. Ferdinand Sauerbach, the Chair of Surgery, called Forssmann into his office and fired him on the spot, stating that while his antics might be good for a circus, that he had no business being in an academic institution. Another surgeon, Willi Felix, agreed to allow Forssmann to continue with his research but only if he catheterized rabbits and other animals. Forsmann, however, continued to catheterize himself, but quit after cutting down on himself nine more times such that there were no more veins to use. Then he was fired again in 1932 for lack of productivity, and eventually became a urologist. (I think this made sense as he must have had a lot of left over urinary catheters at home).

During the war he became a member of the National Socialist Party, the pro-Nazi group, but he was known as a humanitarian and would provide health care to Jewish people despite the Nazi rules. When he was pressured for this action, he joined the German army to avoid being further investigated. Here he was captured by Americans, then escaped across the Elba River only to be captured again and placed in a Russian prison camp until the end of the war. Following the war he was initially not allowed to be a physician, and so he worked briefly as a lumberjack until the early 1950s when he became Chief of Urology in a small town near Frankfurt.

On a day in late October, 1956, Werner Forssmann received a phone call from the Karolinska Institute in Stockholm telling him he had been selected to receive the Nobel Prize in Medicine, and that he would share it with two other individuals, Andre Cournand and Dickinson Richards from Columbia University. His initial response was to ask what he was getting the Nobel Prize for. "I feel like a village parson who has just learned that he has been made bishop", he was reported to say. And so ends the colorful adventure of an obsessive individual who was the first to develop cardiac catheterization, a procedure that helped revolutionize the field of cardiology.

How Should You Prove Your Hypothesis—The Golden Goose and Black Swan Experiments

There are clearly many ways one can go about to test your hypothesis. Before you jump in, I do suggest that you discuss your ideas with people knowledgeable to the field. This is where finding a mentor can be very helpful. Mentors are a secret weapon in discovery, and are often difficult to find. The more open in thinking they are, the better off you will be. They can help guide you and keep you on track.

In that regard, even though it may sound exciting, I do not recommend self-experimentation, and neither do the Human Subjects Committees. You might die, you might get fired, or you could win the Nobel Prize, but it is a little bit like playing roulette. However, all of the other approaches have strengths and weaknesses. So, I recommend trying more than one approach, for if more than one road goes to Rome, your idea becomes all the stronger. Confirmation of your idea using multiple approaches is ultimately the best way to prove your hypothesis. And if it ends up as a treatment that makes people better, then it is a true success.

Finally, my friend Richard (‘Dick’) Glassock, who is an Emeritus Professor of Medicine and has been in academic medicine for many decades, told me that the most important thing to do if you have a novel idea is to perform a “Black Swan” experiment. When I told him I did not know what that meant, this is what he said.

“Rick, most scientists, including you (!), are more interested in proving your idea is right rather than wrong, and so the tendency is to design a “Golden Goose” experiment that if positive supports your hypothesis. However, equally important, or perhaps critical, is to design a “Black

Swan" experiment where the primary goal is to try to prove your hypothesis wrong. The fact is that very few people do these latter studies. This prejudice is one of the reasons so many theories get thrown out over time."

Black Swan experiments are critical because they help keep you from becoming a fanatic who only does studies to strengthen his or her idea, and not to challenge it. But the more common way to do this is to design a study that is both a Golden Goose and Black Swan experiment at the same time. Those experiments are especially nerve-racking. But speaking of animals, there is one animal especially fearsome for discoverers, and that is the Grey Rhino. Big, nearly invisible as it stands behind you in the China shop, but ready to destroy anything without warning. We will learn about this dangerous beast in the next Chapter!

Chapter 9 ..and Get the Discovery Accepted

If you're going through hell, keep going." *Winston Churchill*

"In science the credit goes to the man who convinces the world, not to the man to whom the idea first occurs," wrote Sir William Osler, who is often considered the Father of Modern Medicine. To me this sounds sad, but it is absolutely true that making a discovery is only half of the work, and the other half is convincing the world. Sure, if you introduce a therapy such as insulin that works from the start, your work will be rapidly accepted. But when the discovery is a disruptive innovation, it is often a drawn-out fight. We will need Churchill again to help us ride the storm. Here, I will tell you my approach on how to cross the Valley of Death if you have a disruptive discovery. It begins with knowing who are your enemies.

Identifying Your Enemies

When you have a discovery that will require changing how people think, there will aways be both friends and enemies. Usually there is a subset of people who are open to your ideas and rush you with their interest and excitement, and welcoming these first responders is beneficial. This involves actively responding to their emails and questions, sending them materials and always following the rule that "being friendly pays." Again, do not worry about competition.

There will also be a group of people that will subtly or actively try to dispose of your idea by attacking it, and sometimes even attacking you. Some groups may even hire individuals whose mission is to counter your work.[34]

In some respects, this is a "normal process" when you try to bring a new idea or invention or type of artwork to the field. All new ideas need to be evaluated critically, and this has led to some philosophers like Thomas Kuhn to regard the resistance to new ideas as a normal response. But I prefer not to view it this way, for the resistance, especially for disruptive innovation, is often severe and lifelong, and the discoverer has a good chance to be flattened by a tank if he or she takes this process lightly. Rather, view it as a war. Churchill stated, "You have enemies? Good.

[34] This may sound paranoid, but as part of a lawsuit, I was once privy to seeing such information in which I was one of the targets of such an approach.

That means you've stood up for something, sometime in your life." Churchill was talking about defending democracy during World War II, surviving attacks by the Nazis, and maintaining ones vision to the finish line. Here you are under attack for suggesting a disruptive innovation. The concept is the same. And the first step is to identify thine enemies.

***The Ivory Tower Syndrome**:*

In science there are usually two extremes. On the one end are individuals who are dogmatic and tend to be very rigid in their thinking. Everything is according to the book and there is no freedom for free thought. Typically, these individuals are older and set in their ways. At the other end of the spectrum are the skeptics, who take enjoyment out of challenging the current thinking. Sometimes they consider themselves intellectuals because they like being philosophical and challenging. Many times they are also younger. However, often this can translate into not being decisive and not taking a stance, but rather just trying to identify what could be possibly wrong with an idea.

In essence, both suffer from similar rigidity. As Bertrand Russell wrote, "Dogmatism and skepticism are both, in a sense, absolute philosophies; one is certain of knowing, the other of not knowing." For me, a dogmatic person is one who remains convinced of their way regardless of the data, while a skeptic has no conviction despite all of the data.

When you have a disruptive innovation, these two sides expand from their extreme ends and spread towards the center. The general rule is that the more disruptive the idea, the greater it expands, and if you are lucky enough that there is no longer a middle group that is open to this idea, then you have the whole scientific field believing you are wrong.

Now, the unfortunate aspect of this, is that this is the peer group that tends to evaluate the merit of your science, and they are also often the group that funds your science, as most grants tend to come from the government, and these grants are typically reviewed by "experts in the field." And the farther afield you are from them, the less likely you will succeed. And remember, when you start, that they are in the Ivory Tower, and you are in the field.

The Dark Forces of Industry

The second major opponent is industry. When a discovery adversely affects an industry, there can be a huge attempt at suppressing the inventor/discoverer or his or her data. One way is

to influence the leaders in the field to challenge the idea, and the more important the authorities are, the stronger is the attack. For example, in the early 1930s the way pneumonia was treated was by giving people horse serum that contained antibodies to the specific strain of bacteria. These sera were provided by Lederle, a company that had many horse farms in New York. When the first antibiotic hit the scene in the mid-1930s, the early studies provided spectacular data. However, physicians at Harvard, who had been receiving grants from Lederle, expressed caution and wanted more studies.

The same thing happened in the early 1960s, when the head of the Nutrition Department at Harvard, Fred Stare, was funded secretly by the Sugar Industry to try to champion low fat diets for heart disease, and at the same time to downplay the role of sugar[35]. "Project 226" was one of the culminating achievements, in which Stare and coauthors were funded to publish a large review in the New England Journal of Medicine that downplayed and attacked the scientists that had found sugar could be involved in metabolic disease. The role of the sugar and high fructose corn syrup industries continue to be an issue, and studies have shown that if the authors are funded by the sugar industry, that for some reason the results show that sugar is safe.[36]

Documents from the 1950s show that the primary way industries try to suppress disruptive ideas is to instill doubt, and one of the best ways is to get a physician to provide the argument.[37] This is the method the tobacco industry used to fight the idea that smoking could cause cancer. They will then showcase their idea to the public. As Churchill (see, we like him) said, "There is no such thing as public opinion. There is only published opinion." Of course, there are many other techniques, including lobbying in congress, funding scientists to perform carefully designed experiments to attempt to show their product is safe, and others. But the bottom line is that if your disruptive discovery affects an industry, assume that you are at war.

[35] Kearns CE, Schmidt LA, Glantz SA. Sugar Industry and Coronary Heart Disease Research: A Historical Analysis of Internal Industry Documents. JAMA Intern Med. 2016 Nov 1;176(11):1680-1685

[36]Massougbodji J, Le Bodo Y, Fratu R, De Wals P. Reviews examining sugar-sweetened beverages and body weight: correlates of their quality and conclusions. Am J Clin Nutr. 2014 May;99(5):1096-104.

[37] Saloojee Y, Dagli E. Tobacco industry tactics for resisting public policy on health. Bull World Health Organ. 2000;78(7):902-10.

The Grey Rhino

I can only speak briefly about the Grey Rhino, as it is typically invisible but "lurks in the shadows". In essence we call it a Grey Rhino as it is a dangerous beast that blends into the background so that it is invisible to us. It is there, however, and is always trying to undermine you. Sometimes it may represent someone who outwardly seems to agree with you, and nods with approval when you give a talk. However, the danger is what the grey rhino does when you are not around.

I have seen a Grey Rhino once. I had been invited to be on a board formed by the National Institutes of Health to review grants submitted by scientists and physicians from many Universities throughout the country. These grants often are critical to the scientist, as they provide the funding not just to do the experiments, but also salary support. This is where you can send your new idea and hopefully get it funded. In turn, the Reviewers are supposed to be open minded, but, as we know, may include both dogmatic or skeptical individuals.

One meeting one of the more senior professors stood up and said, "This is a person with a really brilliant new idea. She even has fantastic preliminary data to support her idea, and her experiments seem feasible and achievable. But even though I cannot find anything wrong, there is something that does not feel right, so I cannot support it." That is a Grey Rhino. They smile, tell you you're great, make you feel loved, and then squash, thump and crash. You're dead.

The Enemy Within

I need to mention that you can be your own worst enemy. We talked about you not becoming a fanatic who is consumed by your own hypothesis. No one likes jabberwockies at the dinner table[38]. It is also important to never argue you are "the first". There is a saying, that "if you think you are original, you have not learned how to read German." But it really is true, and Google is a great way to find these earlier reports. But this is not fatal, it is simply the way it is. And many have proposed new ideas but only some have succeeded in getting the views accepted. So if you

[38] A great self-test is to ask you spouse if you are crazy. If she or he says yes, you are at high risk of being a jabberwocky.

have a discovery that adds on to the ideas and work that someone had in the past, it is actually a good sign you might be on to something important. But the key point is that it is rarely helpful to say you are the first, even if you are. And one reason is that it makes people more skeptical of you.

Another aspect, which we stated in the chapter on making discoveries, is you need to remain prepared to adjust or change your hypothesis at all times till the day you die. Remember this key phrase—one should change the hypothesis to explain the data, not change the data to explain the hypothesis. We need to always listen to the negative data and to think about the anomalies not only from the past, but the ones that show up after our hypothesis is out. As Mark Twain wrote, "It aint what you don't know that gets you into trouble, it is what you know for sure that just aint so". As the author Charles Baxter wrote, "When all the details fit in perfectly, something is probably wrong with the story."

Remember that the way you developed your idea was to look for anomalies with the prior studies and try to develop a hypothesis with a better fit. We are not often taught to continue to do this with our own idea, and so we are at risk of becoming the dogmatic enemy of the next generation of thinkers. So, shake it off, and be willing to challenge your own hypothesis, and you might simply amaze the world.

The Art of Winning

"Kites rise highest against the wind - not with it." *Winston Churchill*

Publish

Be prepared for rejection. It is not enough to simply talk about your idea, or put it on the internet, to convince the world, the idea ideally should be published in a well-respected, international, peer reviewed journal. When your idea is novel and disruptive, however, this is not so easy to do, and you are likely to have your idea rejected multiple times. It is easy for me to give an example (I have been rejected a thousand times and over). I do like the way Richard Horton rejects my paper! But follow the rule—just keep trying.

"Dear Dr Johnson, We read your paper with some interest…. Alas, all that is interesting cannot be published in the Lancet." Richard Horton, Editor, Lancet 1995

The novelty-skepticism law. If your paper does get rejected, don't panic, because it can happen to the best. Kary Mullis, who received the Nobel Prize in 1993 for his invention of the polymerase chain reaction in molecular biology that allowed one to study genes like had never been done before, had all of his major papers rejected when he sent them to the top journals such as Science or Nature. So I have coined the phrase, the novelty skepticism law that basically acknowledges that the more novel an idea, the more skeptical the reviewer, and the less likely it will be published in a 'top' journal. But that is ok, just publish it in a reputable journal. Let the followup papers by others get into Nature. They will probably be more receptive then.

The 90 percent rule. Get 90 percent right and have others do the fine tuning. You need to be convinced you have enough proof, but not more. It is easy to keep doing additional experiments, but the goal is to get your paper out once you are convinced. Follow Voltaire's insight "Perfection is the mortal enemy of Excellence. The goal, as my friend Steve Hanley says, is to "Get the Monkeys on the Island," which refers to the concept that you first get a rudimentary colony set up before you eventually build your 5-star resort. Another way of thinking about this is you plant the seed. Sometimes people do this by publishing the hypothesis first. I am nauseatingly famous for doing this—in fact, if you put down hypothesis and Johnson RJ into a pubmed search, you will pull up over 100 papers. Sickening!

Whisper, Don't Bark. When you submit your paper, always understate your story. Remove any idea how it may change the world. Never detail the importance. The goal is to get the paper published, and just describe your findings and rapidly end the discussion. When Watson and Crick published their paper on the structure of DNA, they did not write how important it would be for studying genetics and life, but they did include one sentence that alluded to that, "It does not escape our notice the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." The goal is to get the paper published. Reviewers are more likely to accept it if the message is understated. Whisper the facts. **Then** you can write a review where you can claim how your discovery will save the world.

Be concise. Being concise matters. No one wants to spend a lot of time reading a paper. If it is bathroom reading, it may be just right! So take the time to make it concise and direct. And listen to another rejection of mine from, you know who, the great Dr Richard Horton.

"Dear Dr Johnson, We would contend that if you cannot make your argument succinct then it may not be worth making in the pages of a general medical journal. One should recall that Watson and Crick's description of the structure of DNA was only 900 words long." Richard Horton, Editor, The Lancet July 11, 1996

If you want to someone to hear you, deliver the key message an sit down. Think how short was Lincoln's Gettysburg address. Long talks and long papers are boring. Churchill said it this way, "This report, by its very length, defends itself against the risk of being read." Don't let your work fall in this category.

Persevere. Rejection is common, especially if you have something new. When it happens repeatedly, I usually respond by shortening the paper and removing anything that might lead to additional questions. Just keep the paper direct with what question you are asking and then keep your answers related to the question. Then end the paper. Never bring in new ideas. To get the goal line, you need to focus and finish. And do not worry too much if it gets published in a lowly rated journal. Just get it out, and you have won the first battle.

Lecturing

Bark, don't Whisper. Unlike publishing, where you want to undertstate, when you speak you should try to make the most compelling argument you can give, including with all of the implications for what it means. The approach is by storytelling. As our adviser, Winston Churchill, said, "If you have an important point to make, don't try to be subtle or clever. Use a pile driver. Hit the point once. Then come back and hit it again. Then hit it a third time - a tremendous whack." The goal is to use an attacking style where you emphasize the weaknesses of the current thinking—but never attack the individuals who promote those ideas. So be like the bull fighter, Manolete, in which you attract attention but avoid being hurt. Or, like the Muhammad Ali, you "Float like a butterfly, sting like a bee."

Identify Your Target Audience

One target audience are the scientists or others that are in the field whose viewpoint you hope to change. Know that it is hard to convince the scientists unless you can bring a leader onto your side. This is a very important rule. Sometimes it best works to meet with one of those that have argued against you, and to spend some time showing them your evidence. So often their

rejection of your hypothesis is a "reflex rejection', and when they see the data and talk to you in person, they can be convinced. Once you have a leader convinced in your work, you can join up and publish together. It may happen that in the end that individual is given the most credit for the work, but it is fine, especially if you get the idea accepted. Remember the goal is to convince the world.

The more important group to persuade is the public, and that can be done by lectures, podcasts, youtube or any particular venue. A great example was the 'Low Carb' diet that was introduced by Atkins. So many scientists did not believe in low carbohydrate diets as the field was still focused on low fat diets. But when Atkins book, entitled "Dr. Atkins new Diet Revolution" was published, people tried the diet and saw that it was very effective, and it had a large impact on awakening the world to the idea that people are eating excessive amounts of sugar and carbohydrates.

If You make a Mistake

If you are trying to discover things, it will be inevitable that you make some mistakes. Edison said, "I make more mistakes than anyone else I know, and sooner or later, I patent most of them." Mistakes are not always bad, but they are also not always good. Even great scientists can make mistakes. Linus Pauling, who collected two Nobel Prizes, published a paper in February 1953 in Nature in which he thought DNA consisted of three strands curled around each other (Triple Helix)[39]. But, despite being wrong, he lived to see the day. But mistakes are a risk we take when we try to 'push the envelope' of science. One of the worst was by a team from Northwestern University who reported that preeclampsia, a condition that occurs in pregnancy and results in severe high blood pressure and occasionally seizures, might be due to a worm[40]. Indeed, the authors showed pictures of worm-like organisms in the blood and placenta of patients with preeclampsia. However, later it was shown to be an artifact that happened during the staining of the blood and tissues. So, while I do not want you to overdo this, be brave, be willing to be wrong, be willing to fail. If you do find something that challenges the paradigm, do not be afraid to publish. And if you

[39] Pauling L, Corey RB. A Proposed Structure For The Nucleic Acids. Proc Natl Acad Sci U S A. 1953 Feb;39(2):84-97

[40] Lueck J, Brewer JI, Aladjem S, Novotny M. Observation of an organism found in patients with gestational trophoblastic disease and in patients with toxemia of pregnancy. Am J Obstet Gynecol. 1983 Jan 1;145(1):15-26.

feel squeamish about this, then listen to the sage advice of Mark Twain. If you are concerned that you might be wrong, just "Eat a live frog first thing in the morning and nothing worse will happen to you the rest of the day."

Do You have to Wait till the Old Guard Die?

If you have a disruptive innovation, it is sort of like being Stonewall Jackson, as you may win a lot of battles, but it is hard to win the war. But there is one major way, and that is if your disruptive innovation, invention or idea ends up having a major impact. For example, there may have been pushback from the Old Guard (an affectionate name for the Establishment) to replace the tried-and-true use of horse antibodies to treat infections, but antibiotics were so superior that the use of horse serum therapy for pneumonia rapidly became antiquated and then extinct.

If your idea results in type of meaningful impact, then you can showcase your hypothesis and get it accepted by the world even if the Old Guard continue to shut the door on you. For example, one of the tragedies of developing kidney failure is that the production of red blood cells is impaired, and so patients become anemic, which makes them tired, weak and short of breath. I remember as a young physician how I often had to give blood transfusions every month to my patients with kidney disease just to keep them feeling okay. There was a physician at the University of Washington named Joseph Eschbach who was interested in why kidney failure caused this problem and he became convinced that the kidneys produced a hormone that would stimulate the bone marrow to make red blood cells. But most of the older medical leaders in the country believed the problem was that when the kidney function fails, that toxins are retained that inhibited red cell production. So Joe told me how his grants were always turned down. But somehow he found a way to keep doing research while supporting himself by working part-time in private practice.

Finally, a tiny new company named Amgen announced they had identified the hormone from the kidney, which was named erythropoietin. The Old Guard was still skeotical, saying that giving the hormone would not correct the anemia because the retained toxins would still inhibit the production of red cells. So Amgen asked Eschbach to lead the clinical trial to see if erythropoietin could help treat the anemia of patients with end stage kidney disease. I was in the audience when Eschbach presented the results. I remember the first sentence of his lecture, "Today I am delighted to vindicate a hypothesis that I have carried for many years and which was discarded

by the Establishment…..” It was wonderful to see him rise against the current and to survive the attack. As the saying goes, “Damn the torpedoes, full speed ahead.”

We have taken a whirlwind tour of what discovery is about. Science is not absolute, at least in medicine. Science is a moving needle, and the joy of discovery is figuring out where the needle is pointing. Osler may have captured this entire idea when he said, “The philosophies of one age become the absurdities of the next, and the foolishness of yesterday has become the wisdom of tomorrow”.

Finally, since this is a book on the art of discovery, I think it is useful to end with a story of a disruptive innovation *in process*—meaning that it has not been fully accepted. In the next chapter I will share a story from research I have been involved in, but recognize that I do not equate this story with the *proven* disruptive discoveries that are described earlier in this book. However, the story is somewhat interesting as it represented a series of discoveries, each one with a bigger insight, such that in the end what seemed like a minor initial observation ended up with a discovery that could indeed have a major impact on our overall health. The experts, of course, remain skeptical, and in this case the graphing of the novelty-skepticism coordinates continues to place it off the paper. However, this does not daunt me, for if I follow the rules of being brave, over 90% convinced, and willing to be wrong, then it is worth presenting. So put on your deerstalker hat, get out that pipe, find the armchair, and let’s go! The game is afoot.

Chapter 10 A Personal Story: In Search of King Priam's Treasure

"Silly ants," the grasshopper bellowed, as he looked at the ants scurrying home from his leaf top, "you are always working! Can't you see it is time to play?" He then took his little fiddle and played a few notes.

On the ground below, a long train of ants were headed home, each with a grain or seed held between its jaws. At the end was the littlest ant, who seemed to have the biggest load, one that was even larger than himself. The little guy stopped for a moment and dropped his grain and looked up at the giant grasshopper high in the leaves. "They say winter is coming."

"Ridiculous! Inconceivable!" the grasshopper exclaimed. "Look around. The skies are blue, the sun is high. Food is everywhere. If there is ever a time to play, this is it!" And the grasshopper tapped his foot, and began playing a grasshopper jig.

The little ant listened to the music, began tapping his feet, and looked at his friends. "May be the grasshopper is right. It would be fun to dance!"

"Heed your elders", one of the soldier ants said as he came back to get the little ant back in the line. "There will be time later."

A few weeks went by, and one morning a frost had come, leaving the leaves cold. A shivering grasshopper came out, and looked for food, but there was none to be found. He looked down at the ground, but the ants were not there, although there was a well-worn trail that was easy to see.

"They must have some food," the grasshopper sighed as he followed the frigid trail to the giant anthill at the edge of the forest. As he got closer, he thought he heard music, and when he reached the hill, he could just peer down the little ant hole to see the ants dancing in the candlelight to a type of foot stomping music known as the six-footed greengrass jig.[41] It was a beautiful, happy music, and the grasshopper wanted to stay and listen, but he had to move on, as food was scarce and he was hungry.[42]

[41] As opposed to the bluegrass version.

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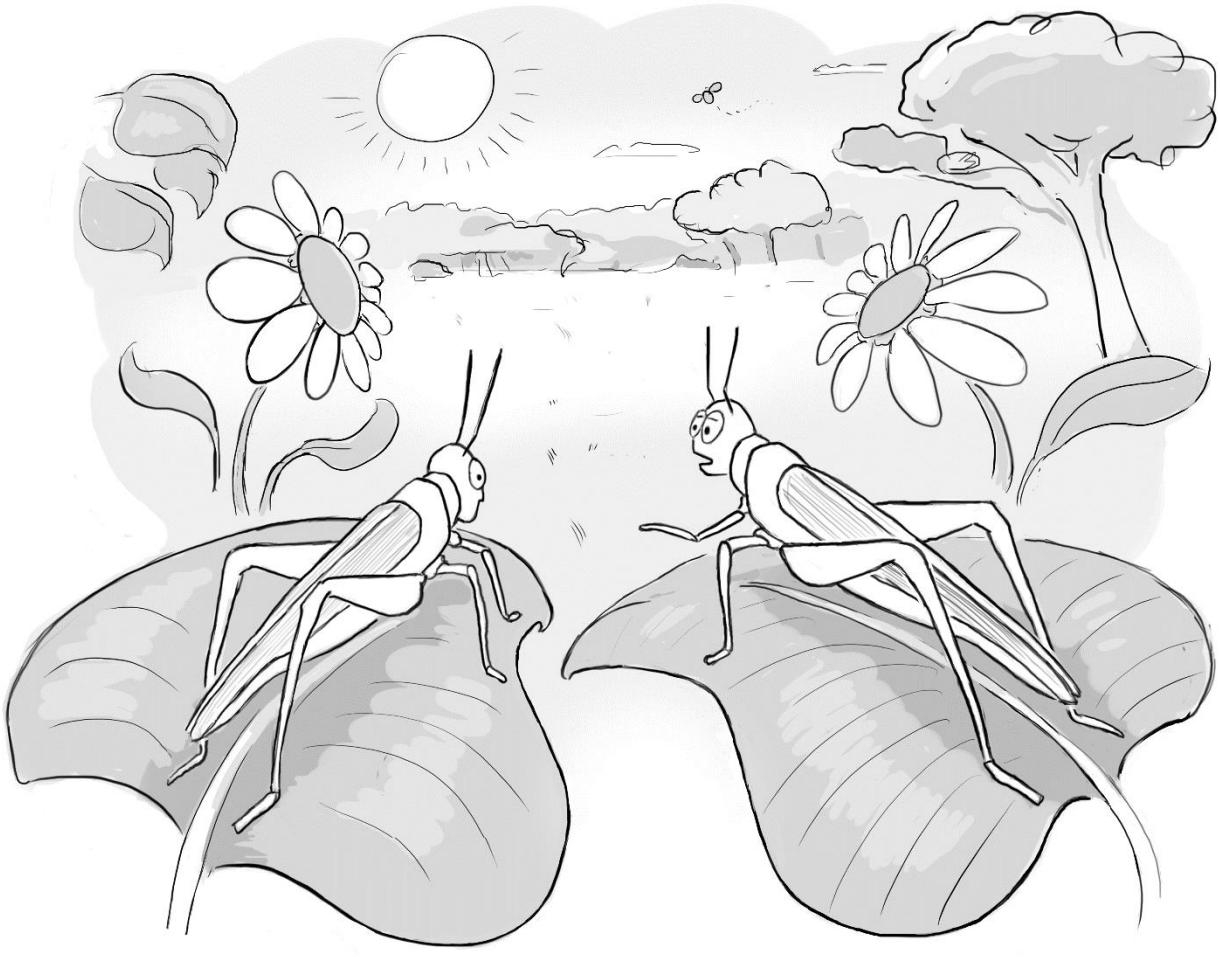


Winter? I mean, have you ever seen proof?

The story of the grasshopper and ant has been told for centuries and is about the importance of being prepared. At one level it is simply contrasting work and play, and the importance of being prepared. One must prepare for the worst when it is still possible, and not at the last minute. At a deeper level, it is about the harshness of nature, and how the difference between life and death depends on whether there is sufficient food during times when food is not available.

Many animals seem to be aware of the importance of storing food to aid survival during harsh times. Not just ants, but chipmunks and deer mice will hoard seeds and nuts in their homes, providing a cache of food that they depend on to survive when times are tough, such as during the winter months. But while storing food in your home is great, it is a bit risky since others might steal it from you. And what if you suddenly have to move due to the nearby presence of a predator? It would be ideal if one could store food and have it always with you, to provide you the nourishment when you need it.

In fact, nature has devised a way an animal can store food and take it with it wherever it goes. It is called FAT. Despite the common view that fat is bad, in nature fat can be a godsend. Fat doesn't just hang on our body, it has an important function. Specifically, when there is no food around, fat is broken down to provide the energy we need. Fat is the backup plan nature uses to help animals when food is not available.

Of course, too much fat is also a problem. If you are the fattest gazelle, that extra weight may make it hard to run as fast as the others, and you might look especially tasty to a cheetah or lion. If you are the last in the pack, you might be the first to be caught. So being too fat can be a detriment, for while you may live the longest during a famine, you might be the first to be on the dinner table in the home of your predators.

But nature is wise, for it has been around a long time and seems to know how best to balance when it is good to be fat and when it is not. Indeed, in nature most animals regulate their weight so they just have a small amount of fat (such as 10 to 15 percent of their body weight), that helps them survive for short periods when food cannot be found. And despite variations in food intake, weight overall remains stable. If an animal eats too much one day, it will eat less the next. Somehow the animal seems to know how not to get too skinny to put its life at risk if food should suddenly be unavailable, and also how not to be too fat so it ends being the first to dinner at the lion's den next door (and I don't mean as a guest).

There are exceptions to this rule, however. Sometimes it is important to get fat, such as when winter is coming. The ants may scurry to find food and store it in their anthills, but a lot of animals just become fat. Beginning a month or two before winter, brown bears will start eating voraciously, and willincrease their weight as much as ten pounds a day. Every year there is a "fat bear" contest on the internet to get a photo of the fattest bear before it hibernates. Then, as winter hits, the bear finds a den, and sleeps throughout the winter without eating or drinking. It will slowly break down the fat as it hibernates, which provides not only the energy it needs to survive, but also the water. Mind you, fat does not contain water, but when it breaks down, it not only produces energy, but also water.

Nature seems to know when it is time to become fat or not. While bears and marmots become fat in the fall so they can hibernate through winter, birds such as the Godwit put on fat prior to their long-distance migrations as they may fly for thousands of miles without stopping for food or water. Other animals, like lemurs and orangutans, gain fat during the wet season and then use the fat to provide calories and water during the dry season when food and water are less plentiful. Some birds, like the Emperor Penguin, will get fat before they nest, for when they are incubating the egg between their feet and their bottom, they have no opportunity to fish. Indeed, females of practically all species tend to need more fat, especially when they are pregnant, as they have to provide the calories the baby needs while it is in the womb or when it is little and breast feeding.

There is one more aspect to this. That is that when these animals start gaining weight, they do not simply eat more and put on more fat. It seems they trigger a whole set of biologic responses. They become persistently hungry and thirsty, they start foraging for food much of the day, but when they are resting they decrease the amount of energy they burn, and they start storing fat not just in their fat (adipose) tissues but also in their liver and blood. This is all part of a survival tactic to maximize their fat stores. They also become 'prediabetic' in which the glucose in their blood starts to rise, and this is associated with less glucose being utilized by the muscle. This is a good thing to do if one is preparing for a famine, as it reduces the amount of fuel (energy) used by the muscles while preserving glucose for the brain, which tends to prefer glucose as its main fuel. Nature seems to know that when there is no food around, that the most important thing is to provide enough fuel to the brain so the animal does the right things at the right time to maximize its chance to survive.

This ability for nature to suddenly switch from a situation in which weight is tightly controlled to one in which the animal is continuously hungry and rapidly becomes fat and prediabetic can happen over days. It is as if nature has developed a *biologic switch* that is turned on at critical times to assist survival. Thus, one could argue that the process of getting fat is a fundamental biological response in nature similar to the "Flight and Fight" response, but this one is triggered *before* the crisis occurs. Just think about this—why would an animal want to store fat if food is available on a daily process?

This can lead to disruptive thoughts.

What if obesity is not just because we like the taste of junk foods and tend to "supersize" our drinks, but rather because a biologic response is telling us that we are hungry and need to eat more? Could it be that when we go back for seconds it is because we are still hungry? What if there is a biologic switch that is responsible, and that we have inadvertently triggered it? Could the obesity epidemic be due to an activation of a "survival switch"? What happened during the twentieth century that suddenly caused obesity and diabetes to increase suddenly? There has also been not only a rise in obesity and diabetes, but also of other diseases, such as high blood pressure, heart disease, liver and kidney disease, cancer, behavioral disorders, and dementia. *What if* the rise in all of these diseases is because we have activated a biological switch that was meant to be beneficial and aid survival, but when put in constant overdrive could be the cause of most of today's diseases? Think of the impact if we could identify what is causing the switch and we could turn it off. It would be like finding ancient Troy and King Priam's treasure!

In the next few pages, I will share the circuitous road we took that led us to what we believe is the identification of this biological switch. I again want to emphasize that this story remains "in evolution", and that it is not widely accepted. This is not unexpected given its disruptive nature. But I feel it is an interesting tale to tell, as it emphasizes many of the principles of the discovery process. Also, as I noted at the end of the last chapter, it is noy my intent to view this as having any equivalence to the proven discoveries discussed earlier in this book, although if the ideas presented turn out to be right, then the impact of this disruptive innovation will be high[43].

A Road with Unexpected Turns and Consequences

[43] For those interested in the story in more detail, consider checking out *The Fat Switch* (2012) or *Nature Wants Us to Be Fat* (2022).

I began my research career studying kidney disease in the laboratory of Dr William Couser at the University of Washington. The research was fun and productive. Typically, we would try to understand the causes of kidney diseases by studying kidney diseases in laboratory mice and rats. I learned almost everything I know about research in Couser's laboratory, and we had many unexpected discoveries that kept the excitement going. I am forever indebted to his wonderful mentorship.

As a kidney doctor, I rarely thought about obesity, at least from the standpoint of research. However, I do have a vivid memory of being at a party at Couser's home when I was approached by a Chinese doctor named Yipu Chen. Yipu was also doing research in the laboratory, and we had become friends. That night, Yipu came up to me and told me that one day I would become a Professor. As a young doctor in the laboratory, I viewed this as a great compliment.

I thought that this compliment must relate to the fact that I had just had one of my research studies published in one of the top scientific journals. Nevertheless, since I like compliments, I turned to Yipu and said, "Thank you, Yipu. Why do you think I will become a full Professor one day?"

"Because you are becoming fat. *Very* fat. And in China, only the full professors get fat."

I looked at myself, and I had been gaining weight. Drat! And I thought Yipu was telling a joke, and perhaps he was, but it was based on truth. For the situation in China had been bad for years under the reign of Mao Tse Tung. Indeed, even in the early 1990s (which is when this conversation happened), the salaries in China were low, and most people barely got by with enough food to live. In medicine, it was only the most successful and wealthy, such as the Professors, who could afford to eat well and get fat.

While the research overall went well, at one point my research funding was on the verge of running out, and while I had enough monies to cover my salary and that of my technician, I had to stop doing experiments in my own laboratory for about four months. I should mention that funding is the greatest challenge for those who do research, and research that tends to be too novel or disruptive is often the toughest to get funded.[44] Nevertheless, persistence is a good survival tactic in the research world.

[44] It has been argued that Columbus' proposal to "find a new route to India by sailing west" would have been turned down without preliminary data that the route exists, See satirical editorial. Petsko GA. Goodbye, Columbus. Genome Biol. 2012;13(5):155.

If you fall into a situation in which you cannot afford to do your own experiments, one trick is to study someone else's experiment. Indeed, I learned there was a scientist named Steve Schwartz who was studying high blood pressure in laboratory rats, and he gave me permission to study the kidneys of those animals. This research interested me, as the cause of most cases of high blood pressure was not known, but there was evidence that it has something to do with the kidneys. In particular, there seemed to be a problem with excreting salt, and it was widely thought that retention of salt in the body was somehow responsible for increasing blood pressure. This is why low salt diets or drugs that stimulate salt excretion (that is, diuretics) are commonly given to people with high blood pressure. Yet no one really understood what the defect in the kidneys were since tests evaluating the function of the kidneys were typically normal..

Nevertheless, when I looked at the kidneys of his rats, I could see that there was subtle damage, so the kidneys weren't normal. The very next day my car broke down when I was driving to Vancouver, and I ended up in a café where I doodled for hours on a napkin while thinking about what might be the cause of high blood pressure. Then, the idea came to me that perhaps the kidneys of people with high blood pressure are initially normal, but that something happens to cause subtle injury that is not enough to be detected by the routine laboratory testing, but perhaps enough to affect the ability of the kidney to excrete salt. I subsequently persuaded Steve to do a study to see if rats with this subtle kidney damage would develop high blood pressure if put on a high salt diet. Bingo, it happened! I had a clue to the cause of high blood pressure. It was time to change the direction of my research.

Only a short while later I had the opportunity to present my research to Jaime Herrera-Acosta, a physician from Mexico City who was an expert on high blood pressure. He was intrigued with my idea and invited my wife and I to go to the Galapagos Islands with him. Accompanying us was Bernardo Rodriguez-Iturbe, who was a kidney specialist from Venezuela. Each day we would explore the various islands and then in the late afternoon, we would sit on the ship deck and talk, and often we would brainstorm about our research. Both Jaime and Bernardo were interested in my idea that subtle kidney damage might be the cause of high blood pressure, but Jaime told me that I was jumping (a phrase I had heard before) and that we needed better measurements and tests to make sure that the findings were consistent with what is observed in patients with high blood pressure, and he offered to do these studies as he had a sophisticated laboratory dedicated to hypertension research. I smiled and agreed. Bernardo asked me how I thought the anatomic

changes in the kidney might lead to salt retention, and he suggested that it might relate to low-grade inflammation that I had found but had pretty much ignored. I thought Bernardo's idea was unlikely, but he bet me and suggested he could do the experiments. I smiled and agreed.

Before I knew it, we were a team, that we called the "Flightless Cormorant Club" after this species of bird that lived on the Islands. The name was not that attractive, so later we simply became the "Tres Mosqueteros".[45] Over the next few years we did many studies to understand the cause of high blood pressure. What we discovered was that the development of hypertension[46] appears to involve two phases. The first phase was driven by some mysterious factor or factors that raised blood pressure and that over time caused subtle kidney damage. The second phase was driven by the kidney damage, and specially by low-grade inflammation in the kidney (that is correct, I lost the bet) that impaired its ability to excrete salt.[47]

But there remained a mystery afoot, as Sherlock might say. What was the mysterious factor that caused the initial phase of hypertension? I had recently seen a paper that reported a strong association of gout with high blood pressure and with kidney disease. Gout is a type of arthritis in which a substance known as uric acid reaches high levels in the blood, to the point that it is higher than its solubility and crystallizes into the joints causing a red, hot, and painful arthritis. I pulled all of the papers I could find on gout and uric acid, and during a very long flight to Australia I read the stack of papers and came up with an idea. Perhaps the way high blood pressure develops is that a person with high blood uric acid forms crystals not only in the joints but also in the kidneys, and that this then causes the low-grade inflammation and kidney damage that leads to salt retention and high blood pressure.

So we decided to raise serum uric acid in the rat and see if we could induce crystal deposition in the kidney, but our initial studies were negative, although interestingly a very mild kidney injury developed. At that point no one wanted to do further studies since the general feeling was that the likelihood that there would be an effect on blood pressure was remote. I was about to end this research when a Brazilian physician named Marilda Mazzali volunteered to repeat the study and see if there was an effect of raising blood uric acid levels on blood pressure.

[45] The Three Musketeers

[46] Hypertension is the official word for high blood pressure.

[47] Bernardo went on to lead many studies with our team to better understand the nature of the inflammation and how it caused the salt retention. The idea that inflammation is responsible for high blood pressure was a disruptive idea that has since been accepted by the medical community.

A few weeks she came back to me with a surprised look. “The rats are developing high blood pressure.” Even though this is what I had hoped for, I was not expecting this, for if an elevated uric acid caused high blood pressure, it seems like it would have been known. So we were very careful and studied a hundred animals or so to make sure we were right. When we looked at the kidneys, we also found the presence of subtle kidney damage. Interestingly, there were no uric acid crystals in the kidney. The way uric acid raised blood pressure appeared to be differebt from what I postulated.

I was now more of a gout doctor than a high blood pressure doctor. I was soon joined by others, including Gaby Sánchez-Lozada (who took over Jaime’s laboratory after his untimely death) and Duk-Hee Kang (who had been in my laboratory but continued her research when she went back to Seoul, Korea). Rapidly we learned that uric acid was not simply an inert waste product that causes arthritis, but that it has biological functions including the ability to cause inflammation and oxidative stress. It seemed that these latter effects were causing our blood vessels to constrict and our blood pressure to rise.

One missing piece of evidence was whether uric acid might be causing high blood pressure in people. It was around that time I moved to Houston to work at Baylor College of Medicine. One day my dream came true—a young pediatric kidney specialist named Dan Feig came to my office. He was running a high blood pressure clinic, for while type 2 diabetes and high blood pressure were classically diseases of adults, they were now occurring more commonly in children. We both realized that if a high uric acid might have a role in the first phase of hypertension, that the ideal group to study would be people who have not had high blood pressure very long. And who would be better to test than children with newly diagnosed high blood pressure?

Dan went on to show that the children developing high blood pressure almost inevitably had elevated blood uric acid levels—moreover, when he lowered the uric acid in a well designed clinical trial, the blood pressure normalized in nearly 90 percent of the kids. It was a eureka moment.

Then Dan and I read the old literature, and we found that the idea that uric acid might be a cause of high blood pressure was not new. Indeed, high blood pressure was discovered in the 1870s by a medical resident named Frederick Mahomed who was in training at Guy’s Hospital in London, and in his original paper he found an association with gout. He even suggested that an

elevated blood uric acid might be the cause of high blood pressure.[48] Later, in 1897, Nathan Davis, the President of the American Medical Association, gave his presidential lecture in which he suggested that gout likely caused high blood pressure by inducing subtle changes in the kidneys[49]. So much for originality! However, this idea disappeared from the medical literature during the early 1900s.

I again moved, this time to the University of Florida in Gainesville. Now there was a new question. What was causing the elevated blood uric acid levels in the children who were developing high blood pressure? It seemed unlikely to be alcohol, red meat or shellfish, which are the usual suspects that raise uric acid and cause gout. However, one possibility was sugar, as sugar contains fructose, and fructose raises uric acid. Intake of sugar and another sweetener, high fructose corn syrup (HFCS), had also risen in the twentieth century, and this was also associated with a parallel rise in blood uric acid levels and high blood pressure. Could sugar, and particularly fructose, be a major cause of high blood pressure?

Takahiko Nakagawa, a young assistant professor in my group, then performed a series of studies in which he administered fructose to laboratory rats. Fructose raised uric acid, increased blood pressure, and caused mild kidney damage in rats, and when we gave a drug to prevent the uric acid from going up, the animals were protected and did not develop high blood pressure. Hurray! Our hypothesis was right! Sugar intake raises uric acid which causes salt retention and raises blood pressure. All we need to do is to cut back on these two white powders to prevent high blood pressure, and this might help reduce the risks for stroke, heart failure and kidney disease!

But Taka had a bigger finding, one that was unexpected and far more interesting. For when he gave fructose to the rats, the rats also developed obesity, elevated blood fats, and insulin resistance. That was not what was unexpected, as sugar (for which fructose is a component) was widely suspected to be a cause of obesity. Rather, the surprise was that lowering the uric acid significantly blocked these findings. Rats were less fat and insulin resistance was minimal. And what was special about this is that the effect of fructose to raise uric acid is not at all related to the calories in fructose.

At this point we knew that obesity from sugar intake was not just due to excessive calorie intake, but that it had something to do with uric acid. It was around this time that I became puzzled,

[48] Mahomed, F.A., *On chronic Bright's disease, and its essential symptoms.* Lancet, 1879. **I**: p. 398-404.
[49] Davis, N.C., *The cardiovascular and renal relations and manifestations of gout.* JAMA 1897. **29**: p. 261-262.

as here we were finding that an elevated uric acid was having a role not only in gout, but in high blood pressure, obesity and diabetes, yet humans were known to have higher blood uric acid levels than most other mammals. Indeed, some studies had shown that most mammals degrade uric acid using a special enzyme that is present in their livers, but humans lost the ability to degrade uric acid millions of years ago due to a mutation in the gene controlling that enzyme, such that now the only way to rid our uric acid is via the urine or gut. The fact that the mutation is present in all humans today further suggested that it must have had some type of survival advantage. But how can we explain this if uric acid is bad?

My reading suggested that the mutation occurred approximately 12 million years ago during a period known as the mid-Miocene. It appeared to have been a tumultuous period in which global cooling was occurring, and nearly 30 percent of all species became extinct. I reached out to an anthropologist named Peter Andrews at the Museum of Natural History in London who was an expert on our primate ancestors during this time in history. He expressed interest in this topic, and so I flew to London to meet him, and in a very treasured afternoon we brainstormed together in his office at the Museum.

Peter explained how the first apes originated in Africa where they lived primarily on fruit, and that when global cooling occurred in the early Miocene, that the sea levels fell, opening a land bridge from Africa to Eurasia. Across this land bridge travelled many animals, among which were our ancestors. For several million years some of our ancestors lived in Europe and Asia Minor, but as global cooling worsened, it was no longer possible to eat fruit all year long due to the change in vegetation, which was unlike Africa which was still warm enough such that some fruit could always be found. Andrews had documented that the apes in Eurasia suffered from starvation during the cooler months, and this forced them to come out of the trees and to look for alternative foods such as roots and tubers. During this time there were a lot of evolutionary changes, with changes in the skeleton and teeth. Eventually things got so bad that all of the apes in Eurasia disappeared. But Andrews, as well as others, had found fossil evidence that some of the ancestral apes made it back to Africa where they evolved into the African Great Apes and into Humans, while some of the ancestral apes migrated to southeast Asia to become the orangutan. Since both groups shared the same mutation in uric acid, it meant that the mutation had to come from a common ancestor, and that must have been in Eurasia during the period of starvation. We had a clue!

I then told him our half of the story, which is that fructose, which is the primary sugar in fruit, seemed to have a special role in stimulating fat, and that we had found that this was dependent on the ability of fructose to make uric acid. Then came the question, what if the mutation in uric acid caused a greater rise of uric acid in response to fructose, as the enzyme to degrade it would be gone. Would that lead to more production of fat in response to a set amount of fructose? Could it be that, as fruits became less available, that the mutation might have provided a boost in fat production that could help the animals survive the cooler times of the year?

Studies were then done that confirmed these ideas. For example, Gaby found that if she inhibited the uric acid enzyme, that laboratory rats would gain weight and fat with even small doses of fructose. A more exciting study was done by Eric Gaucher, Miguel Lanaspa and others, in which the extinct gene was resurrected, and we could show that its presence dampened the effect of fructose to increase liver fat. We had proof—the mutation that occurred 12 million years ago made us super-sensitive to fructose and saved our species.

Now things were beginning to fall in place. In our remote past our ancestors got into trouble when changing climates caused food shortages that occurred primarily during the cooler months. It must have been a desperate time, and Peter was even involved in the discovery of nine of these ancestors who appeared to have died together, likely from starvation. It was in this setting where a mutation occurred that led to not only higher uric acid levels, but also to a greater increase in body fat in response to fructose. Having this mutation helped the animals store fat better than those lacking the mutation over the cooler when food was less available, and over a relatively short period, only those ancestors carrying that mutation survived. While this mutation helped prevent starvation, it was not enough to cause obesity, and through the next millions of years, it just passed from generation to generation. But then, around 500 B.C., some farmers discovered a grass growing along the Ganges River that created a sweet liquid when it was boiled. Soon this syrup from the sugarcane was recognized as being like “honey without the bees”. At first sugar was prohibitively expensive, and only the rich could afford it. As it became less expensive, it became more available for everyone. Per capita intake per year increased from 4 pounds in 1700, to 18 pounds in 1800, to 90 pounds in 1900, to about 150 pounds currently. And, maestro, now we have the obesity epidemic!

Fructose was suddenly becoming important in the biology of survival and to be important in both nature and evolution. It was time to become a naturalist. We began studies of hibernating

squirrels[50] (with Chris Rivard) and the hibernating Swedish brown bear (with Peter Stenvinkel and Ole Fröhbert). One of the striking things about the bears is that during the fall, they start eating huge amounts of ripe fruit (not like the few we eat daily), so that the amount of fructose was high. Similarly, on reviewing the literature, it seemed that nectar (which is essentially fructose-laden sugar) was the primary food used by hummingbirds, and how it was associated with an increase in liver fat and blood sugar that would develop by the end of the day, only to largely recover during the night when the bird's high metabolism would burn off the fat. Other animals also seemed to use fruits to increase their body weight, such as the orangutan and lemur. Yet, not all animals were eating fructose. For example, if fructose is the cause of obesity, how does a penguin get fat?

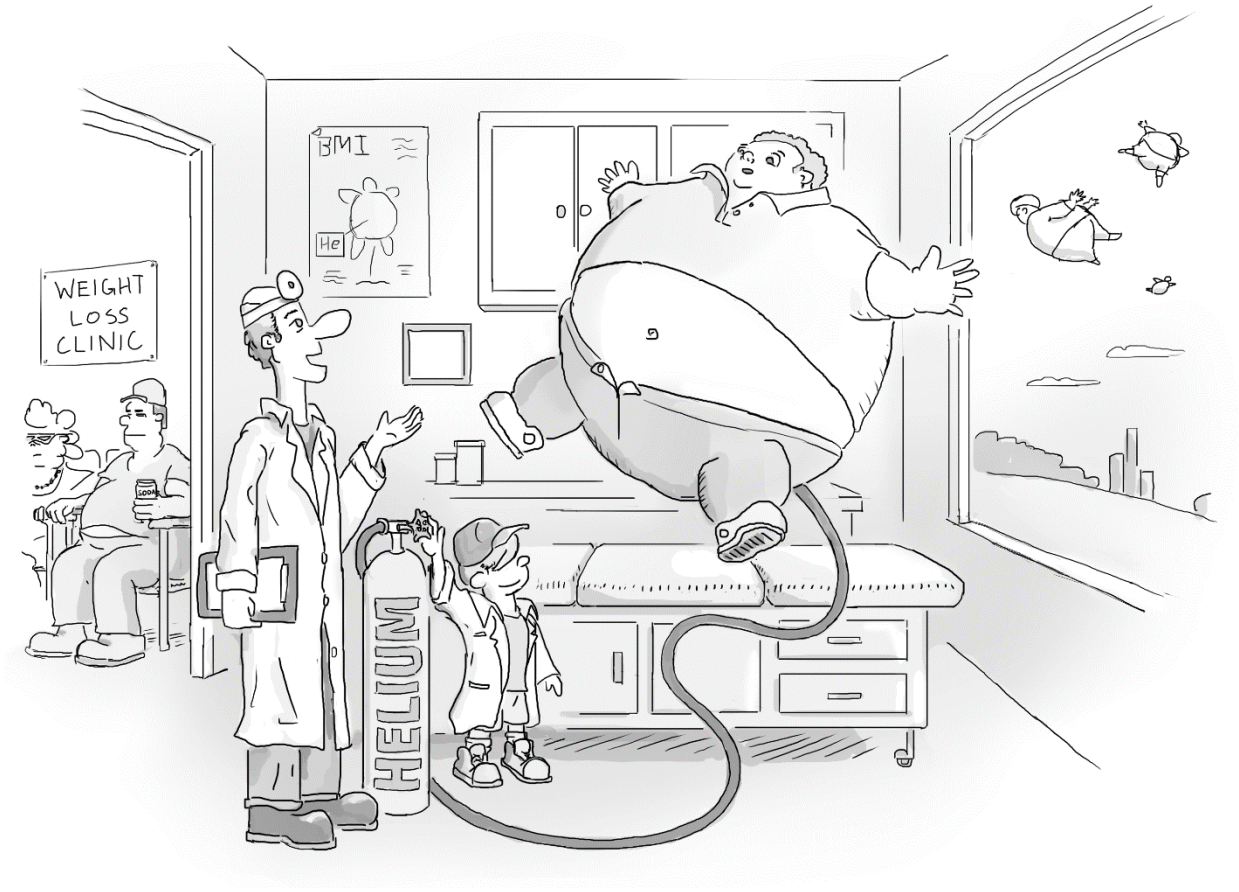
The solution to this vexing question came when I was brainstorming with Miguel Lanaspa. All of our focus had been on sugar and high fructose corn syrup, for these foods were the major source of fructose, and even makes up as much as 15 percent of our daily caloric intake. But *what if* fructose could be made in the body? Indeed, it had been known that fructose can be made from glucose through a chemical reaction called the polyol pathway. The main way this was known to occur is when glucose levels are high, such as in diabetes. But what about people who did not have diabetes. Did they make fructose?

Miguel then suggested a brilliant idea. Could fructose production in the body occur when people eat starchy foods like rice and bread? It is known that the blood glucose goes up after a meal after eating these foods.[51] *What if* the temporary rise in blood sugar in a meal could cause a burst of fructose to be produced in the body? Would that be enough to activate this biological switch?

We then did a number of studies in laboratory animals and found strong evidence that the body does make fructose from carbohydrates, and that this is a major way carbohydrates cause obesity. This could also explain why low carbohydrate and keto diets were so effective at lowering weight.

[50] We studied these little guys in a hibernaculum which is a place where light and temperature are carefully adjusted to mimic winter hibernation. When these guys enter the "torpor" state, they become mini-rock statues. It is quite impressive.

[51] Foods that raise blood glucose after a meal include sugar, bread, rice, potatoes and cereal. The Dark Five!



It is not the sugar that makes you heavy. You have an 'element deficiency'.

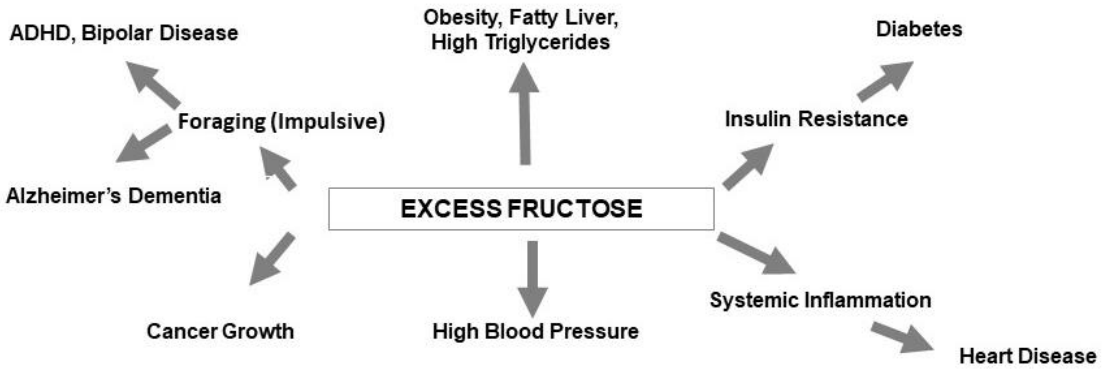
We also realized that the polyol pathway, the enzyme system that converts glucose to fructose, was activated by conditions associated with stress—such as by mild dehydration, when oxygen levels or low, or when an animal is physically stressed. We also found that certain foods rich in salt and uric acid, as well as alcohol, could also activate the switch. In essence, fructose is produced from glucose when an animal is stressed, which makes sense since fructose is the nutrient that activates the survival pathway.

It seemed we had uncovered a fundamental survival pathway in the biology of life. But why was fructose so different from other foods? This super important question was addressed by both Gaby and Miguel[52]. What they found is that the way most foods work is that they are converted to active energy (which is called ATP[53]) and once ATP levels are sufficiently high, the animal is satisfied and quits eating. However, when fructose is given, the uric acid is produced and blocks the production of ATP, so the active energy falls in the cell. This creates an alarm signal that the animal is in a low energy state, and triggers hunger, foraging and food intake. The animal then eats more, but the calories are preferentially stored as fat (stored energy) since there is a problem producing the active energy (ATP). Eventually the ATP levels are restored, but at the expense of an overall increase in fat.

You might think this story should end, but we then began to realize that many of the important diseases of the day could be linked with overactivation of the survival pathway. For example, we linked chronic stimulation of foraging with an increased risk for behavioral disorders (especially attention deficit hyperactivity disorder and bipolar disorder) and dementia. Specifically, to forage one has to be impulsive, reduce one's self control, and not focus but to constantly search and move. This effect actually requires reducing the activity of the brain in certain regions, which if occurs chronically and repeatedly, can lead to behavioral changes and/or even dementia. Indeed, I worked with famous neurologists such as David Perlmutter and Dale Bredesen that helped identify evidence that fructose (both from the diet and also from fructose produced in the brain) is likely involved in the cause of Alzheimer's disease. We and others also found that the fructose pathway was involved in heart, liver and kidney disease, with high blood

[52] It is also important to note that many other outstanding scientists have also identifed key mechanisms by which fructose acts, including Samir Softic, Mark Herman, Lewis Cantley and Marcus Goncalves.
[53] Adenosine Triphosphate

pressure, and even with some cancers. More recently we discovered that alcoholism is driven in part by the effects of alcohol to stimulate fructose production.



So why is this story not uniformly accepted? Of course there are many arguments, but the two major ones are that as the story keeps expanding, and as it becomes more and more important, it becomes increasingly difficult to believe that one pathway could be so important. It even makes me wonder! It is almost like a Pandora's box, for the evils released from excessive fructose appear to involve way more diseases than we bargained for. The second, more important reason, is that the ultimate proof will require studies in humans once inhibitors of fructose become clinically available. Recall that what made Banting's research so compelling was when he administered insulin to a boy with diabetic acidosis. So lets hope that day comes soon.

In summary, it has been a long and circuitous journey, one that began with a loss of funding and ended with the discovery of a basic survival mechanism used in nature. Our work does suggest that the obesity and diabetes epidemics are the result of an activation of this survival mechanism that was aimed to protect us from starvation. The mechanism is quite successful at making us fat, but unfortunately, instead of hibernating, we just keep activating the switch. The consequence is that we are now suffering from a lot of metabolic diseases, from diabetes to cancer. Unfortunately, it is hard to prevent this switch from being activated, as so many foods activate the switch. Low carbohydrate and keto diets should work the best.

Darn, my research is wrecking my appetite. But Mark Twain said it best. "The only way to keep your health is to eat what you don't want, drink what you don't like, and do what you'd rather not do."

Chapter 11 The Exhilaration of Discovery and Why Being a Discoverer Matters

"All you need in this life is ignorance and confidence; then success is sure."

Mark Twain

There is a story, which may or may not be true, but for which it really does not matter. According to the legend, a fundraising dinner was held in Washington D.C. to benefit a charity. Among the various guests who attended the benefit, there were two Nobel Laureates, and they sat together at the dinner. During the evening they could not help but notice that an older man sitting at their table was almost continuously approached by people who wanted his autograph. Eventually one of the Nobel Laureates turned to him, and said,

"Pardon me, but may I ask you your name?" To which, the man smiled and said, "Clint Eastwood."

The Nobel Laureates looked at each other, both a bit mystified, and then one said, "Well we could not help but notice that there seem to be a lot of people who want your autograph. Could you be an actor?"

Clint looked at them, squinted his eyes a little, and then said, "Are you guys for real?"

Now I tell this story for two reasons. First, the story seems funny as it emphasizes that scientists often live in their own world and sometimes have very little knowledge of current events, sports, and film.

But you may have also noticed that I did not provide the names of the Nobel laureates. And that is because whenever I hear the story, it seems no one remembers their names. And it emphasizes a key point, which is that if you want to be famous, go into art, sports or film. Do not be a scientist. The beauty of science is in the fun of looking for treasure, or the desire to be like Sherlock Holmes or Indiana Jones. Discovery will not make you famous. Artists can be immortal, but scientists not.

The real excitement is in the quest, and in the actual making of a discovery. There is an exhilaration that comes with making a discovery that is hard to describe, as it not only is a joy similar to solving a puzzle, but it often opens an entire new way of viewing things. A discovery is

like seeing the world through new eyes, as it expands the mind, and leads to more rather than fewer questions. And questions are what fuels discoveries, so one discovery will likely lead you to more!

Let me end with some final advice from Winston Churchill, our not-so-secret hero. He wisely said, "We make a living by what we get, but we make a life by what we give." So, keep your eyes open, believe in yourself and look for that next discovery. It will be fun, exhilarating, and who knows? It is possible your discovery might make a difference. And even if not, you are attempting to better understand the world, and to potentially help it.

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