[Excerpt from *Happy Accidents: Serendipity in Modern Medical Breakthroughs*]

Introduction

Serendipity, Science's Well-Guarded Secret

Contemplating the genesis of the great medical breakthroughs of the last century, most people picture brilliant, well-trained scientists diligently pursuing a predetermined goal—laboriously experimenting with first this substance and then that substance, progressing step by step to a "Eureka!" moment when the sought-after cure is at last found. There in the mind's eye is Marie Curie stirring a vat of pitch-blende over many years to recover minute amounts of radium, or Paul Ehrlich testing one arsenical compound after another until he finds Salvarsan, the "magic bullet" against syphilis, on his 606th attempt. In the contemporary setting, one looks to what might be called Big Science. Surely, we imagine, in the halls of ivy-draped universities and the gleaming labs of giant pharmaceutical companies, teams of researchers in smart white coats are working in harmony to cure cancer, banish the common cold, or otherwise produce the Next Big Thing in medicine.

For its own reasons, the medical establishment is happy to perpetuate these largely false images. By tradition and protocol, it presents science as a set of facts and strong beliefs that, like the Ten Commandments, have been set in stone by a distant all-knowing authority and, if followed, will lead inevitably through a linear process to the desired results. Furthermore, it portrays the history of scientific advances as a sequence of events that have led to more-or-less direct progress.

The reality is different. Progress has resulted only after many false starts and despite widespread misconceptions held over long periods of time. A large number of significant discoveries in medicine arose, and entirely new domains of knowledge and practice were opened up, not as a result of painstaking experimentation but rather from chance and even outright error. This is true for many of the common drugs and procedures that we rely on today, notably many antibiotics, anesthetics, chemotherapy drugs, anticoagulant drugs, and antidepressants.

Consider the following examples, all typical of how things happen in medical research:

- At the Johns Hopkins Hospital in 1947, two allergists gave a new antihistamine, Dramamine, to a patient suffering from hives. Some weeks later, she was pleased to report to her doctors that the car sickness she had suffered from all her life had disappeared. Drs. Leslie Gay and Paul Carliner tested the drug on other patients who suffered from travel sickness, and all were completely freed of discomfort, provided the drug was taken just before beginning the potentially nauseating journey. A large-scale clinical trial involving a troopship with more than 1,300 soldiers crossing the rough North Atlantic for twelve days (Operation Seasickness) decidedly proved the drug's value in preventing and relieving motion sickness. Dramamine is still used today, available over the counter.

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- A similar circumstance proved very beneficial to the neurobiologist David Anderson of the California Institute of Technology, who publicly announced his serendipitous breakthrough in the *New York Times* in July 2001. Researching neural stem cells, the cells that build the nervous system in the developing embryo, Anderson discovered the "magic fertilizer" that allowed some of them to bloom into neurons, sprouting axons and dendrites: "It was a very boring compound that we used to coat the plastic bottom of the Petri dish in order to afford the cells a stickier platform to which to attach. Never would we have predicted that such a prosaic change could exert such a powerful effect. Yet it turned out to be the key that unlocked the hidden neuronal potential of these stem cells."

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THE NORMAL VERSUS THE REVOLUTIONARY

In his highly influential 1962 book *The Structure of Scientific Revolutions*, Thomas Kuhn contributed an idea that changed how we see the history of science. Kuhn makes a distinction between "normal" and "revolutionary" science. In "normal" science, investigators work within current paradigms and apply accumulated knowledge to clearly defined problems. Guided by conventional wisdom, they tackle problems within the boundaries of the established framework of beliefs and approaches. They attempt to fit things into a pattern. This approach occupies virtually all working researchers. Such efforts, according to Nobel laureate Howard Florey, "add small points to what will eventually become a splendid picture much in the same way that the Pointillists built up their extremely beautiful canvasses."

Kuhn portrays such scientists as intolerant of dissenters and pre-occupied with what he dismissively refers to as puzzle-solving. Nonetheless, a period of normal science is an essential phase of scientific progress. However, it is "revolutionary" science that brings creative leaps. Minds break with the conventional to see the world anew. How is this accomplished? The surprising answer may be "blindly"! Systematic research and happenstance are not mutually exclusive; rather they complement each other. Each leads nowhere without the other.

According to this view, chance is to scientific discovery as blind genetic mutation and natural selection are to biological evolution. The appearance of a variation is due not to some insight or foresight by rather to happenstance. In groping blindly for the "truth," scientists sometimes accidentally stumble upon an understanding that is ultimately selected to survive in preference to an older, poorer one.

As explained by Israeli philosophers of science Aharon Kantorovich and Yuval Ne'eman, "Blind discovery is a necessary condition for the scientific revolution; since the scientist is in general 'imprisoned' within the prevailing paradigm or world picture, he would not intentionally try to go beyond the boundaries of what is considered true or plausible. And even if he is aware of the limitations of the scientific world picture and desires to transcend it, he does not have a clue how to do it."

An anecdote about Max Planck, the Nobel Prize-winning physicist, hammers home this reality. When a graduate student approached him for a topic of research for his Ph.D. thesis, asking him for a problem he could solve, Planck reportedly scoffed: "If there was a problem I knew could be solved, I would solve it myself!"

Induction and deduction only extend *existing* knowledge. A radically new conceptual system cannot be constructed by deduction. Rational though can be applied only to what is known. All new ideas are generated with an irrational element in that there is no way to predict them. As Robert Root-Bernstein, physiology professor and author of *Discovering*, observed, "We invent by intention; we discover by surprise." In other words, accidents will happen, and it's a blessing for us that they do.

The Receptive Scientific Mind

"Accident" is not really the best word to describe such fortuitous discoveries. Accident implies mindlessness….A better name for the phenomenon we will be looking at in the pages to follow is "serendipity," a word that came into the English language in 1754 by way of the writer Horace Walpole. The key point of the phenomenon of serendipity is illustrated in Walpole's telling of an ancient Persian fairy tale, *The Three Princes of Serendip* (set in the land of Serendip, now known as Sri Lanka): "As their highnesses traveled, they were always making discoveries, *by accidents and sagacity*, of things they were not in quest of."

Accidents *and* sagacity. Sagacity—defined as penetrating intelligence, keen perception, and sound judgment—is essential to serendipity. The men and women who seized on lucky accidents that happened to them were anything by mindless. In fact, their minds typically had special qualities that enabled them to break out of established paradigms, imagine new possibilities, and see that they had found a solution, often to some problem other than the one they were working on. Accidental discoveries would be nothing without keen, creative minds knowing what to do with them.

The term "serendipity" reached modern science by way of physiologist Walter B. Cannon, who introduced it to Americans in his 1945 book *The Way of an Investigator*. Cannon thought the ability to seize on serendipity was the mark of a major scientist. The word is now loosely applied in the popular media to cover such circumstances as luck, coincidence, or a fortunate turn of events. This sadly distorts it. Serendipity means the attainment or discovery of something valuable that was not sought, the unexpected observation seized upon and turned to advantage by the prepared mind. The key factor of sagacity has been lost. Chance alone does not bring about discoveries. Chance with judgment can.

Serendipity implies chance only insofar as Louis Pasteur's famous dictum indicates: "In the field of observation, chance favors only the prepared mind." Salvador Luria, a Nobel laureate in medicine, deemed it "the chance observation falling on the receptive eye." *I have the answer. What is the question?* Turning an observation inside out, seeking the problem that fits the answer, is the essence of creative discovery. Such circumstances lead the astute investigator to solutions in search of problems and beyond established points of view.

The heroes of the stories told in this book are not scientists who merely plodded rationally from point A to point B, but rather those who came upon X in the course of looking for Y, and saw its potential usefulness, in some cases to a field other than their own. Chance is but one element, perhaps the catalyst for creativity in scientific research. And, yes, the process of discovery is indeed creative. It involves unconscious factors, intuition, the ability to recognize an important anomaly or to draw analogies that are not obvious. A creative mind is open and can go beyond linear reasoning to think outside the box, look beyond conventional wisdom, and seize on the unexpected. Most important, a creative scientific mind recognizes when it is time to start viewing something from a whole new perspective.

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The New Science of Bacteriology

The meteoric rise of Robert Koch (pronounced “coke”) from obscure country doctor to international celebrity was based on his talent for developing techniques for the isolation and identification of microbes. When he was a young physician in a small town near the German-Polish border, his wife bought him a microscope for his birthday, and he started looking at microbes as a pastime in a makeshift laboratory partitioned from his living room by a dropped sheet. By 1876, at the age of thirty-three, he had discovered the bacterium that causes anthrax. Within two years he published his monumental paper *Investigations Concerning the Etiology of Wound Infections*, scientifically proving the germ theory beyond doubt.

Koch’s landmark papers generated much excitement because he transformed the concept of what caused so many diseases. He would go on to establish with the clarity and purity of Euclidean logic the essential steps (“Koch’s postulates”) required to prove that an organism is the cause of a disease: that the organism could be discoverable in every instance of the disease; that, extracted from the body, the germ could be produced in a pure culture, maintainable over several microbial generations; that the disease could be reproduced in experimental animals through a pure culture removed by numerous generations from the organisms initially isolated; and that the organism could be retrieved from the inoculated animal and cultured anew.

His painstaking work transformed bacteriology into a scientifically based medical discipline. In 1891, three years after the Pasteur Institute was established in Paris, the German government founded the Koch Institute for Infectious Diseases in Berlin under his directorship. In this era of European imperialist expansion into Africa, Asia, and the Indian subcontinent, he discovered the bacillus that causes cholera and studied the disease known as sleeping sickness in East Africa. Within a few years, through his pioneering methods, the bacterial causes of a host of other diseases—diphtheria, typhoid, pneumonia, gonorrhea, meningitis, undulant fever, leprosy, plague, tetanus, syphilis, whooping cough, and various streptococcal and staphylococcal infections—were uncovered, largely by his students.

An earlier chance observation by Koch had resulted in a critical breakthrough in culturing microorganisms. Up to this point, scientists had grown bacteria in flasks of nutrient broth. In the lab Koch just happened to notice that s lice of old potato left on a bench was covered in spots of different colors. He placed a spot from the potato slice on a slide and saw that all the microorganisms were identical and clearly different from those in another spot. He realized that each spot was a colony of a specific microorganism. The importance of this observation was that in broth all types of microbes are randomly mixed together and only with great difficulty can be selectively cultured. The potato allowed discrete colonies of separate bugs to grow, enabling distinction and selection from culturing for identification and testing. Serendipity pointed the way to obtain pure cultures.

The next step was to develop a more usable culture medium. Adding gelatin to the liquid broth resulted in a solid medium. A tiny loop of platinum wire was used to capture a droplet from a broth containing various species of bacteria, and it was streaked across the surface of the solid broth plate. But much to Koch's disappointment, the gelatin liquefied when placed in an incubator. His colleague, Richard Julius Petri, designed a shallow flat round dish with a cover, and agar, a jelling compound derived from Japanese seaweed, was used as the solid growth medium. Koch came upon this in an indirect way. Japanese seaweed was suggested by the wife of a colleague who had been posted in the Dutch East Indies; she had used it for making jam. In this way was born the Petri dish or "agar plate," the mainstay of a bacteriology laboratory. Clinical specimens such as throat swabs, sputum, or blood are streaked over the surface of the agar and then incubated at body temperature. Colonies containing millions of microbes shortly grow. The technique was revolutionary. Pure cultures of bacteria could now be obtained, enabling their isolation and identification.

Once he had a mechanism with which to isolate microorganisms, Koch was able to identify organisms that caused specific diseases. At this time he began focusing his attention on tuberculosis. Classically referred to as "consumption," human tuberculosis was then responsible for one in seven of all European deaths. Identifying the organism was challenging work over a four-year period. The tiny rod-shaped organism was difficult to recognize with the staining techniques available at the time. Fortunately, a new advance came to Koch's attention. Paul Ehrlich, a young physician with a passion for chemistry, had developed a tissue stain called methylene blue. It was this stain that Koch used to detect the tiny rod-shaped bacillus in the tissues infected with tuberculosis. Because the bacillus grows slowly, it required the addition of blood serum to the agar as a nutrient and incubation for several weeks before colonies became apparent.

In 1882, in an evening address to the Berlin Physiological Society, Koch—now employed by the Imperial Health Office—thrilled the audience with the news that he had discovered the bacillus that causes tuberculosis, *Mycobacterium tuberculosis*. Koch's singular discovery led to his winning the Nobel Prize in 1905.

Inspired by Koch's success with the methylene blue stain, Ehrlich went on to devise and develop, over the years 1878-88, the technique of counterstaining, whereby the washing of a stained specimen with a second, acidic chemical removes the color from only specific cells or parts of cells and thus permits greater differentiation. He experimented unsuccessfully with a number of dyes to stain the TB bacillus until, after a few months, chance intervened. Finishing up his work late one night, Ehrlich found the small iron stove in his home laboratory a handy place to leave his stained preparations to dry overnight. The next morning, before the scientist was up, his housekeeper lit the stove without noticing the glass slides lying atop it. Upon entering the laboratory, Ehrlich was aghast at the sight of the fire in the stove. He rushed to pick up his slides and inspect them through his microscope. What he saw was astonishing. The tubercle bacilli stood out wonderfully in bold color. The accidental heating had fixed the stain to the waxy-coated TB bacteria, allowing ready microscopic identification. This "acid-fast" staining technique is still used today.

Meyers, Morton A. Happy Accidents: Serendipity in Modern Medical Breakthroughs. New York: Arcade Publishing, 2007.