

# Additional Tales of Discovery Through Abductive Reasoning

Discovery commences with the awareness of anomaly ... and it closes only when the paradigm theory has been adjusted so that the anomalous becomes the expected.

— Thomas Kuhn (*The Structure of Scientific Revolutions* (1962))

# Preamble

The present volume entitled, *Additional Tales of Discovery Through Abductive Reasoning*, is a companion to the more extensive, *Exemplary Tales of (Mostly) Nineteenth Century Medical and Epidemiological Discovery Through Abductive Reasoning*. The latter emphasized the career contributions of some fifteen major medical researchers from the end of the eighteenth century (Edward Jenner) to the early part of the twentieth (Charles Nicolle). In contrast, the emphasis in the current volume is more on singular discoveries chosen mostly from the twentieth century that typically involve several individuals (for example, the development of insulin as a way of controlling diabetes, or in the construction of the first antimicrobial sulfa drug).

The various subjects covered in this companion volume are typically indexed by an approximate date as to when something was first discovered or developed. Most topics are concerned with:

- (1) medically relevant substances or procedures (such as in the use of anesthesia or the discovery of a specific antibiotic);
- (2) medical theories for why something occurs (such as in the development of childhood rickets or how cell-mediated immunity operates);
- (3) short tales of medical and industrial product development (such as the invention of gas lighting or gene editing through CRISPR);
- (4) brief stories of scientific discovery (such as the law of universal gravitation or the identification of elements such as oxygen).

Consistent with the larger parent volume, the explanatory approach taken here is one of “abduction” as propounded by Charles Sanders Peirce. As Peirce definitively stated in 1903: “every single item of scientific theory which stands established today has been due to abduction.” As typically framed, Peirce’s form of abductive inference or reasoning can be phrased succinctly as follows:

The surprising fact,  $B$ , is observed

But if  $A$  were true, then  $B$  would be a matter of course

Therefore, there is reason to suspect that  $A$  is true

As an example, suppose we observe that the lawn is wet when going out for the paper in the morning. If it had rained last night, it would be unsurprising that the lawn is wet; therefore, by abductive reasoning, the possibility that it rained last night is reasonable or plausible. Obviously, abducing rain last night from the evidence of a wet lawn could be a false conclusion – even in the absence of rain, some other process such as the presence of dew or automatic lawn sprinklers may have resulted in the wet lawn.

Abduction is a form of logical inference that goes from an observation to a hypothesis that accounts for the observation and which explains the relevant evidence. Peirce first introduced the term “abduction” as “guessing” and said that to abduce a hypothetical explanation, say  $A$ : “it rained last night,” from an observed circumstance, say  $B$ : “the lawn is wet,” is to surmise that  $A$  may be true because then  $B$  would be a matter of course. Thus, to abduce  $A$  from  $B$  involves determining that  $A$  is sufficient or nearly so for  $B$  to be true, but not necessary for  $B$  to be true.

The subsequent verification stages that may follow the identification of an abductive conjecture can typically be phrased in syllogistic terms. Assuming  $A$  represents the explanatory conjecture for our original “surprising” observation, let  $B'$  now indicate some further observation(s) or experimental outcome(s) that should be obtained if  $A$  were true. If  $B'$  does occur, then the conjecture  $A$  becomes even more plausible (and “stays in the running,” so to speak). If, however,  $B'$  does not occur, the conjecture  $A$  does not then appear to be true. This situation possibly leads to the formation of an alternative explanatory hypothesis and/or to a rethinking that  $A$  being true should have led to  $B'$  being true.

To give a sense of how abduction might be explained in the general scientific literature, the author asked the current version 4 of ChatGPT to “write about Peirce’s theory of abductive reasoning.” The following response was generated:

Charles Sanders Peirce, an American philosopher, logician, and mathematician, developed the theory of abductive reasoning as part of his broader work on logic and scientific methodology. Abduction, often referred to as “inference to the best explanation,” is one of the three types of reasoning that Peirce identified, alongside deduction and induction.

Key Aspects of Peirce’s Abductive Reasoning:

Nature of Abduction:

Abduction is the process of forming a hypothesis to explain a surprising or puzzling observation. It involves generating a plausible explanation for a given set of facts, even when there isn’t enough information to guarantee its truth. Unlike deduction, which derives specific conclusions from general premises, and induction, which generalizes from specific cases, abduction starts with an incomplete set of observations and seeks the most likely explanation.

Logic of Discovery:

Peirce emphasized that abduction is the starting point of scientific inquiry. It's the method by which new ideas and hypotheses are generated. He considered it crucial for the creative aspect of scientific discovery, as it allows scientists to make educated guesses that guide further investigation and experimentation.

Generative and Fallible:

Abduction is inherently fallible. The hypotheses generated through abduction are not guaranteed to be true; they are provisional and subject to testing and verification. However, abduction is valuable because it generates new ideas and leads to the formulation of hypotheses that can be tested through deduction and induction.

Pragmatic Aspect:

Peirce's philosophy of pragmatism, which asserts that the meaning of a concept lies in its practical consequences, underpins his view of abduction. He believed that the best hypotheses are those that lead to fruitful and practical outcomes, meaning that they can be tested and potentially confirmed through experience and experimentation.

Creative Insight:

Abduction involves a creative leap or insight, where the thinker connects seemingly unrelated facts into a coherent explanation. This makes abduction distinct from the more mechanical processes of deduction and induction. It's a form of reasoning that is closely related to human intuition and creativity.

Iterative Process:

In Peirce's view, scientific inquiry is an iterative process where abduction, deduction, and induction work together. Abduction generates a hypothesis, deduction derives predictions from the hypothesis, and induction tests those predictions against empirical data. The results of this process may lead to the refinement or rejection of the hypothesis, prompting a new cycle of abduction.

Example of Abductive Reasoning:

Consider a situation where you walk into a room and see that the floor is wet. You might generate several possible explanations: the roof could be leaking, someone might have spilled water, or it could have just been mopped. Abductive reasoning is the process of considering these possibilities and selecting the one that seems most plausible based on the available evidence.

Impact and Influence:

Peirce's concept of abduction has had a significant impact on various fields, including philosophy, artificial intelligence, and cognitive science. It has been particularly influential in discussions about the logic of scientific discovery, the nature of hypothesis formation, and the role of creativity in reasoning. Abduction continues to be a central topic in discussions about how we generate explanations and develop new theories in both everyday reasoning and scientific practice.

In summary, Peirce's theory of abductive reasoning provides a framework for understanding how we generate and refine hypotheses in the face of incomplete information. It underscores the importance of creativity and pragmatism in the process of inquiry, making it a fundamental concept in both philosophy and the sciences.

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## Part I

# MEDICALLY RELEVANT SUBSTANCES AND PROCEDURES

# Chapter 1

## A Few Notable Uses of Plants in Medicine (From Antiquity)

Success in research needs four Gs: Glück, Gesuld, Geschick and Geld [luck, patience, skill, and money].

— Paul Ehrlich (1854–1915)

In addition to the two medically important drugs of quinine and cocaine discussed elsewhere, there are literally hundreds of medicinal substances having plant origins that were known and used for thousands of years before the common era (BCE). Much of this knowledge was codified by the Greek physician and botanist, Pedanius Dioscorides (40–90 AD), in a massive five-volume encyclopedia about herbal medicines and related medicinal substances entitled *De materia medica* (On Medical Material). This pharmacopeia describing over a thousand remedies based on some six hundred plant products was widely read in various translations for some 1,500 years. For several millennia Dioscorides himself was the most prominent writer on plant drugs and how they could be prepared and used.

The original abductive reasoning that may have first led to the identification of particular plants and their medicinal properties has

long been lost to history. Nevertheless, there is one general purpose abductive reasoning paradigm pertinent to most plant-derived drugs developed from the early 1800s onward that is directed toward identifying and isolating the specific chemical substance (alkaloid) responsible for any medicinal effects a plant might have. This generally appropriate abductive reasoning scheme can be phrased as follows:

Surprising observation, B: this particular plant has a “surprising” effect on humans (as typically witnessed through indigenous practice);

Conjecture, A: if there is a specific chemical substance in the plant that produces the observed human effect, then this surprising observation B would be a matter of course;

Therefore, there is reason to believe that the plant contains a chemical substance that produces the effect seen in humans.

Verification of this line of abductive reasoning proceeds by actually isolating a substance from the plant and then using it by itself and without any associated plant preparations to produce the desired effects in humans. In addition to this first verification step, there may be an additional process developed for artificially synthesizing the substance itself from elemental sources without a reliance on plant derivatives.

As discussed in the chapter emphasizing the two drugs of quinine and cocaine derived from plant sources native to South America, their chemical isolation was first performed in the 19th century. The two French chemists, Pierre Pelletier and Joseph Caventou, isolated the quinine alkaloid from the powdered bark of the Chinchona tree in 1820. The German chemist, Albert Nieman (1834–1861), performed

a similar extraction of cocaine from coca leaves for his doctoral thesis in 1860. As important as these two extractions were, probably the most significant and earliest such isolation was done for the plant alkaloid of morphine extracted in 1804 from the opium poppy by the German pharmacist, Friedrich Sertürner, and named after *Morpheus*, the Greek god of sleep. The opium poppy was known for many centuries as a plant that could be used to induce drowsiness, relieve pain, and serve as a surgical analgesia. As the well-known Seventeenth Century English physician, Thomas Sydenham (1624–1689), famously stated: “Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium.”

There are many more specific instances of plant inspired abductive reasoning in the development of drugs that are still in wide use today. One prominent example is Aspirin, the ubiquitous pain reliever and fever reducer derived from the chemical salicin as found in the bark of the white willow. Aspirin was produced in Germany by the Bayer pharmaceutical firm in the late 1800s and soon became one of the most widely used and prescribed drugs ever. The second instance we discuss of abductive reasoning in drug discovery is in the identification of digitalis from the Foxglove plant. Digitalis is still in use today to treat congestive heart failure and/or heart rhythm problems. It acts by increasing blood flow throughout the body and reduces as a diuretic any swelling (edema) that may be present, particularly in the hands and feet. We begin with the story of Aspirin, still one of the most commonly used drugs in the world.

The bark of the willow tree has been known as a medicine for

pain relief and fever reduction (an antipyretic) for several thousand years. It appears, for example, in the Egyptian scrolls known as the *Ebers Papyrus* dating from around 1500 BCE. Of primary interest here, however, is a more recent rediscovery and ensuing abductive conjecture as carried out by the English clergyman, Edward Stone (1702–1768). As the story is usually told, Stone was walking one day in 1763 through a meadow near Chipping-Norton in Oxfordshire while suffering from the agues (the type of intermittent fever caused by malaria). Stone was prompted to cut off and chew a small piece of bark from a white willow tree and was “surprised” at its extremely bitter taste. Remembering that Jesuits’ Powder obtained from the bark of the Peruvian Cinchona tree had a similar taste, Stone (abductively) conjectured that the willow bark might have the same curative powers. He proceeded to dry and pulverize the willow bark into a powder that could be given to individuals suffering from the type of fever symptoms common in malaria. Although Stone was incorrect about willow bark being a general antimalarial, its fever reducing effects did mask some of the common malaria symptoms. Stone continued his experimentation with the pulverized willow bark and eventually produced a letter that was published in the *Philosophical Transactions of the Royal Society* in 1763. The beginning part of that letter is reproduced below:

XXXII. An account of the success of the bark of the willow in the cure of agues. In a letter to the Right Honourable George Earl of Macclesfield, President of R. S. [Royal Society] from the Rev. Mr. Edward Stone, of Chipping-Norton in Oxfordshire

My Lord, Among the many useful discoveries which this age hath made, there are very few which, better deserve the attention

of the public than what I am going to lay before your Lordship. There is a bark of an English tree, which I have found by experience to be a powerful astringent, and very efficacious in curing aguish and intermitting disorders. About six years ago, I accidentally tasted it, and was surprised at its extraordinary bitterness; which immediately raised [in] me a suspicion of its having the properties of the Peruvian bark. As this tree delights in a moist or wet soil, where agues chiefly abound, the general maxim, that many natural maladies carry their cures along with them, or that their remedies lie not far from their causes, was so very apposite [appropriate] to this particular case, that I could not help applying it; and that this might be the intention of Providence here, I must own had some little weight with me.

One salient aspect of Stone's abductive reasoning about willow bark being helpful in curing ague was in his use of the Doctrine of Signatures. In the form adopted by Stone, this Doctrine states that God ensures that natural maladies carry their cures along with them, or at least they are present not too far away. Thus, the willow is common in wet marshy areas where the ague is also prevalent. Another contention in this pseudoscientific Doctrine is that herbs resembling a part of the body can be used by herbalists to treat ailments that reside in and affect those same body parts. For example, because the birthwort plant resembles a uterus, it can be used in pregnancies even though the birthwort is now known to be carcinogenic and highly damaging to the kidneys.

In 1828 the German pharmacist, Johann Buchner (1783–1852), working at Munich University isolated the active ingredient in willow bark and named the crystalline substance salicin after *Salix*, the Latin term for the willow genus. A decade later in 1838, the Italian

chemist, Raffaele Piria (1814–1865), converted salicin into salicylic acid which proved to be even more effective in pain and fever relief although it was often harsh on a person’s stomach. In 1897, Felix Hoffmann (1868–1946), working as a chemist for Bayer pharmaceuticals created acetylsalicylic acid (ASA) by chemically modifying salicylic acid. Supposedly, Hoffmann sought for his father who suffered from rheumatism a less irritating substance with the same effects as salicylic acid. Bayer trademarked the name “Aspirin” for ASA in 1899 and began selling it as a powder. It was the first commercially available non-steroidal anti-inflammatory drug (NSAID) as well as the first drug made synthetically. For the rest of the colorful history regarding the birth of Aspirin and the further development of the nascent pharmaceutical industry, the reader is referred to Diarmuid Jeffreys (2004), *Aspirin: The Remarkable Story of a Wonder Drug* (Bloomsbury, New York).

It deserves mention that a less benign drug than Aspirin, called heroin because of the heroic feelings it produced in a person, was synthesized from morphine by Bayer in 1897 and brought to market about the same time as Aspirin. On August 21, 1897, just eleven days after Hoffman had synthesized Aspirin, he produced heroin by trying to acetylate morphine. His original objective was to produce codeine, a constituent of the opium poppy that was similar to morphine but less potent and less addictive. Instead, the acetylated form of morphine (Heroin) was about twice as potent as morphine itself. Bayer trademarked the drug using the capital “H” and marketed it as an over-the-counter morphine substitute for cough suppression that supposedly did not have morphine’s addictive side-effects. Unfortu-



nately, among its users Heroin would soon have one of the highest rates of addiction ever seen for any drug.

The cardiac drug digitalis as present in the Foxglove herb was identified by the English physician and botanist, William Withering (1741–1799), while working in the area of Birmingham, England, in the 1770s. In his 1785 publication, *An Account of the Foxglove, and Some of Its Medical Uses*, Withering indicates how the Foxglove was first brought to his attention and how he abductively reasoned about the herb being a cure for dropsy (edema) now known to be a common symptom of congestive heart failure:

It was a circumstance of this kind which first fixed my attention on the Foxglove.

In the year 1775, my opinion was asked concerning a family receipt [recipe] for the cure of the dropsy. I was told that it had long been kept a secret by an old woman in Shropshire, who had sometimes made cures after the more regular practitioners had failed. I was informed also, that the effects produced were violent vomiting and purging; *for the diuretic effects seemed to have been overlooked*. This medicine was composed of twenty or more different herbs; but it was not very difficult for one conversant in these subjects, to perceive, that the active herb could be no other than the Foxglove [italics added for emphasis about the “surprising” observation that Withering noticed].

Withering’s text consists of many clinical cases and observations about the use of the Foxglove which we now know contains the heart medication digitalis (digoxin). These cases include many patients treated by Withering himself as well as some from his physician colleagues. What follows is one representative report from a surgeon, Mr. K. Freer, in Birmingham:

Nov[ember], 1780. Mary Terry, aged 60. Had been subject to asthma for several years; after a severe fit of it her legs began to swell, and the quantity of urine to diminish. In six weeks she was much troubled with the swellings in her thighs and abdomen, which decreased very little when she lay down: she made not quite a pint of water in the twenty-four hours. I ordered her to take two spoonfuls of the infusion of Foxglove every three hours. By the time she had taken eight doses her urine had increased to the quantity of two quarts in the day and night, but as she complained of nausea, and had once vomited, I ordered the use of the medicine to be suspended for two days. The nausea being then removed, she again had recourse to it, but at intervals of six hours. The urine continued to discharge freely, and in three weeks she was perfectly cured of her swellings.

In his 1936 text, *William Withering: The Introduction of Digitalis Into Medical Practice*, Louis Roddit comments on the similarity between Withering's (abductive) reasoning with the Foxglove and William Jenner's connections between having had the cowpox and smallpox vaccination, as discussed in the larger companion volume:

The knowledge of the use of foxglove in dropsy may have been known in household medicine in that part of England just as a knowledge that cowpox protected against smallpox was known in Gloucestershire long before the time of Jenner. It needed a man like Withering to study in a scientific manner the effects of this rural remedy and introduce it to the pharmacopeia just as Jenner had taken the countryside tradition of cowpox and by study and observation developed the practice of smallpox vaccination from it.

There are literally hundreds of drugs derived from plant products that could be discussed in ways that directly parallel the narratives

for Aspirin and digitalis. One excellent and very readable survey of the whole field is available in Norman Taylor (1965), *Plant Drugs That Changed The World* (Dodd, Mead, & Company, New York). We end our discussion in this chapter by listing just a few of the medicinal substances derived from plant sources and their alkaloids that have interesting side stories. The reader may wish to pursue these and others described by Taylor further, or to explore the histories behind familiar and pleasurable alkaloids such as caffeine and nicotine, or those that are more deadly such as strychnine, hemlock, and various arrow poisons like curare.

reserpine: This drug is derived from the roots of the Indian snakeroot shrub (*Rauwolfia serpentine*), a member of the notorious dogbane genus. It has been part of Indian medicine (referred to as Ayurvedic) for many centuries and was used to treat snake bite, “moon disease” (or lunacy), and generally to serve as a tranquilizer to relieve psychotic symptoms such as those present in schizophrenia. The reserpine alkaloid was isolated in 1952 and synthesized in 1958 although the later process is still so expensive that extraction from the basic snakeroot is still performed. In more recent uses it has served as a treatment for high blood pressure (hypertension), as an alternative to various antipsychotic medicines such as chlorpromazine (Thorazine), and is generally considered a tranquilizer and mild depressant. It was, for example, chewed extensively by Mahatma Gandhi for such soothing and antihypertensive effects.

ephedrine: Shen Nung was a mythical Chinese ruler, supposedly active around 2500 BCE. He is considered the father of Chinese medicine and responsible for medicinally identifying hundreds of herbs

by personally testing their effects on himself. Nung is viewed as the author of the earliest Chinese pharmacopoeia which included the use of the shrub *Ephedra sinica* (mahuang, in Chinese) for respiratory and bronchial troubles such as asthma. The plant alkaloid of ephedrine present in the *Ephedra* herb was first isolated in 1887, but it was not used as a general stimulant and blood pressure increaser in the western world until the 1920s. In the late 1950s and after, the negative side effects of ephedrine usage became apparent in an increased risk of stroke and heart attack. Many countries including the United States have bans on the sale of over-the-counter dietary supplements containing ephedrine and/or on its employment as a performance enhancer in athletic competition. It is still generally available by prescription as a bronchodilator for asthma and to treat chronic obstructive pulmonary disease (COPD).

progesterone: This particular steroid is a sex hormone produced naturally in the human body and is crucially involved in the female menstrual cycle, pregnancy, and embryo development in humans and other animal species. Although a naturally produced hormone, progesterone can also be obtained from certain plant sources such as the native Mexican yam (*Dioscorea mexicana*) which contain specific organic steroidal compounds called sapogenins (or diosgenins). The synthetic process of producing progesterone from these plant steroids was developed in the late 1930s by the American chemist, Russell Marker (1902–1995), through a three-step process that is still called Marker Degradation. In the years right after World War II, Marker along with several other investors set up the Mexican company called Syntex to produce large quantities of progesterone from the rather enormous Mexican yams available regionally. Given this

increased availability of progesterone, various other products could now be mass-produced such as cortisone, and, as noted below, the first oral contraceptive to be placed on the market.

Although there are no remnants left of any specific abductive reasoning engaged by Marker in his development of the process for turning plant steroids into progesterone, the field of human contraception itself does offer a few. For example, Norman Taylor in his book, *Plant Drugs That Changed the World*, comments on the rhythm method of contraception by indicating one crucial Hindu abductive conjecture regarding female ovulation:

The Roman Catholic Church cannot be naive enough to think they originated the so-called rhythm method, for it is nothing new. Hindu medical schools, around 500 B.C., were advocating the “impregnation is impossible during about twelve days of the menstrual cycle.” Biologically this may be nearly correct, but restraint is easier to advocate than to observe..

Following on the old concept of the rhythm method, a “surprising” observation was made in 1956 by Gregory Pincus (1903–1967) at the Worcester Foundation for Experimental Biology. One of the drugs derivable from the Mexican yam and progesterone could stop ovulation; and most importantly, this drug could be taken orally instead of by injection. The subsequent introduction of the first oral contraceptive, Enovid, marked the beginnings of rational family planning that is the standard for today.

santonin: This is an antihelminthic remedy (that is, a means to eliminate parasitic worms) first isolated in the 1830s by German chemists from *Artemisia cina*, a plant found in Turkmenistan. It acts by paralyzing the front end of a worm while stimulating the back so the

worm cannot maintain its position within the host's intestines. Some type of purgative such as castor oil, can then be used to directly flush the still living worms out of a host's system.

## Chapter 2

# Medicinal Substances From the Ergot Rye Fungus (*Claviceps purpurea*) (Nineteenth Century)

It gave me an inner joy, an open mindedness, a gratefulness, open eyes and an internal sensitivity for the miracles of creation ... I think that in human evolution it has never been as necessary to have this substance LSD. It is just a tool to turn us into what we are supposed to be.

— Albert Hofmann (1906–2008)

Ergotism refers to the constellation of symptoms seen in humans and animals from ingesting the ergot fungal bodies that can infect a variety of grains but particularly rye. Although evidence exists for epidemics of ergotism throughout most of ancient history, it became prevalent in Europe from at least the Middle Ages, manifesting with two prominent symptomatic forms that could occur separately or together. One form commonly found east of the Rhine River was termed “convulsive,” and included painful spasms and seizures along with several mental disturbances such as mania, psychosis, and hallucination. A second form more prevalent west of the Rhine was “gangrenous,” where the ergot alkaloids produced serious vasoconstrictions [restrictions of blood flow] particularly in the peripheral

structures of the arms and legs. This condition often led to the loss of whole limbs without bleeding.

During the various ergotism epidemics that occurred in Europe from the Middle Ages onward, a “surprising” observation was made about a secondary effect of ingesting ergot fungal bodies. Pregnant animals, especially pigs and presumably humans who ate a tainted diet of infected rye grain or bread, spontaneously aborted. The ensuing abductive conjecture reached and passed along informally throughout Europe to the then all-female cadre of practicing midwives was that the ergot fungus provided a means for producing uterine contractions. It became common practice for a midwife to administer several ergot fungal bodies to induce and/or speed labor along. A written documentary source for this practice was available by the year 1582 in a revised German botany book on herbs (called the *Kräuterbuch*) by Adam Lonicer (1528–1586). He wrote about the medical use of ergot as follows:<sup>1</sup>

... they are held to be a special medicine for women in labor and for the purpose of awakening the pains three of the spurs are swallowed ...

The American physician, John Stearns (1770–1848), is typically given credit for introducing ergot into orthodox clinical obstetrics through a letter published in 1808 in the *New York Medical Repository*. The first part of this letter follows:

Account of the *Pulvis Parturiens* [powder for giving birth], a Remedy for quickening Childbirth

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<sup>1</sup>It is of some interest to note that three of the ergot fungal bodies contain about one-half milligram of ergometrine, the usual dose of this alkaloid used in obstetrical practice to induce or hasten labor.



In a letter from Dr. John Stearns, of Saratoga county, to Mr. S. Akerly, dated Waterford, January 25, 1807, is the following narration:

In compliance with your request I herewith transmit you a sample of the *pulvis parturiens*, which I have been in the habit of using for several years, with the most complete success. It expedites lingering parturition [the birth process], and saves to the accoucheur [male midwife] a considerable portion of time, without producing any bad effects on the patient. The cases in which I have generally found this powder to be useful, are when the pains are lingering, have wholly subsided, or are in any way incompetent to exclude the foetus [sic]. Previous to its exhibition it is of the utmost consequence to ascertain the presentation, and whether any preternatural [extraordinary] obstruction prevents the delivery; as the violent and almost incessant action which it induces in the uterus precludes the possibility of turning. The pains induced by it are peculiarly forcing; though not accompanied with that distress and agony, of which the patients frequently complain when the action is much less. My method of administering it is either in decoction or powder. Boil half a drachm of the powder in half a pint of water, and give one third every twenty minutes till the pains commence. In powder I give from five to ten grains; some patients require larger doses, though I have generally found these sufficient.

If the dose is large it will produce nausea and vomiting. In most cases you will be surprised with the suddenness of its operation; it is, therefore, necessary to be completely ready before you give the medicine, as the urgency of the pains will allow you but a short time afterwards. Since I have adopted the use of this powder I have seldom found a case that detained me more than three hours. Other physicians who have administered it concur with me in the success of its operation.

...

Somewhat later in 1822 another American physician, David Ho-

sack (1769–1835), well-known for being the doctor who ministered to Alexander Hamilton and the fatal injuries he incurred after his famous duel with Aaron Burr (1804), commented differently about the safety of ergot, presumably because of the great number of stillbirths and fatal uterine ruptures then being seen with its use:

The ergot has been called, in some of the books, from its effects in hastening labour, the *pulvis ad partum* [powder to aid birth]; as it regards the child, it may, with almost equal truth, be denominated the *pulvis ad mortem* [powder to aid death]; for I believe its operation, when sufficient to expel the child, in cases where nature is alone unequal to the task, is to produce so violent a contraction of the womb, and consequent convulsion and compression of the uterine vessels as very much to impede, if not totally to interrupt, the circulation between the mother and child.

Although the administration of ergot during labor was generally abandoned by the end of the Nineteenth Century, its important use for controlling hemorrhage after delivery continued for some years thereafter.

There are well over fifty ergot alkaloids that can be isolated from the basic rye fungus, all with varying degrees and forms of medicinal effect.<sup>2</sup> One of these alkaloids still in use to facilitate the delivery of the placenta and to prevent bleeding after childbirth is called ergometrine. It was isolated by several different groups of researchers around 1935. For the task of inducing or speeding up labor, ergometrine has been superseded by a synthetic version of oxytocin, the naturally occurring hormone responsible for controlling the process of labor and delivery as well as for various aspects of maternal

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<sup>2</sup>As an example, the ergot alkaloid called ergotamine is often combined with caffeine to manage and treat acute migraine headaches.

and female sexual behavior. The common brand name for synthetic oxytocin is Pitocin, a name that is familiar to many of us who have been a witness to the birth of our own children since the 1960s.<sup>3</sup>

There is a relevant side story about the discovery of oxytocin that involves some abductive reasoning about a pregnant cat. It was Henry Dale (1875–1968) who first extracted the hormone to be called “oxytocin” from the pituitary gland of a mammal, which in this case was from the gland of an ox. When given to the particular animal model being used, which was that of a cat who happened to be pregnant, the “surprising” observations were made of feline uterine contractions. Dale named the substance common to all mammalian pituitary glands “oxytocin,” after the Greek word *oxutokia*, meaning “swift delivery.” Somewhat later, Dale also found that oxytocin assists in the release of a mother’s milk by contracting the smooth muscle around the mammary glands so that milk is “let-down” into the nipple.

Albert Hofmann (1906–2008) was a Swiss chemist employed by the pharmaceutical company Sandoz, which was part of Novartis. He was charged in his position with the task, among others, of researching derivatives of lysergic acid, a common part of all ergot alkaloids. In looking for a marketable analeptic [a substance that stimulates the central nervous system in general and respiration and circulation in particular], Hofmann first synthesized in 1938 lysergic acid diethylamide (LSD), but then set it aside for some five years. Coming back to a resynthesis in April of 1943 and apparently because

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<sup>3</sup>A substance that can be used to induce labor or to prevent *post partum* hemorrhage is generally referred to as an oxytocic. Thus, oxytocin and ergometrine are both oxytocic.

of some minimal skin absorption through his fingertips, witnessed in himself the following “surprising” effects:<sup>4</sup>

Last Friday, April 16, 1943, I was forced to interrupt my work in the laboratory in the middle of the afternoon and proceed home, being affected by a remarkable restlessness, combined with a slight dizziness. At home I lay down and sank into a not unpleasant, intoxicated-like condition characterized by an extremely stimulated imagination. In a dreamlike state, with eyes closed (I found the daylight to be unpleasantly glaring), I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors. After some two hours this condition faded away.

From these initial “surprising” effects that Hofmann felt, he (abductively) conjectured that the synthesized (LSD) substance had more unknown psychoactive effects. To test this hypothesis explicitly Hofmann purposely administered to himself what he thought would be a minimal dose; and, as they say, the rest is history — Hofmann had the first ever LSD or “acid” trip. In some of his own words given in a highly abbreviated form below, Hofmann described the first intentional LSD experience:

... By now it was already clear to me that LSD had been the cause of the remarkable experience of the previous Friday, for the altered perceptions were of the same type as before, only much more intense. I had to struggle to speak intelligibly. I asked my laboratory assistant, who was informed of the self-experiment, to

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<sup>4</sup>For a more thorough story about LSD and Hofmann’s experiences, see Albert Hofmann’s book, *LSD: My Problem Child*. The date on which Hofmann took his first intentional LSD dose (April 19, 1943) is commonly referred to as “Bicycle Day” to indicate of how he got himself home. April 19th is still celebrated by some under this name in honor of Hofmann’s discovery of LSD.

escort me home. We went by bicycle, no automobile being available because of wartime restrictions on their use.

On the way home, my condition began to assume threatening forms. Everything in my field of vision wavered and was distorted as if seen in a curved mirror. I also had the sensation of being unable to move from the spot. Nevertheless, my assistant later told me that we had traveled very rapidly. Finally, we arrived at home safe and sound, and I was just barely capable of asking my companion to summon our family doctor and request milk from the neighbors. In spite of my delirious, bewildered condition, I had brief periods of clear and effective thinking — and chose milk as a nonspecific antidote for poisoning.

The dizziness and sensation of fainting became so strong at times that I could no longer hold myself erect, and had to lie down on a sofa. My surroundings had now transformed themselves in more terrifying ways. Everything in the room spun around, and the familiar objects and pieces of furniture assumed grotesque, threatening forms. They were in continuous motion, animated, as if driven by an inner restlessness. The lady next door, whom I scarcely recognized, brought me milk — in the course of the evening I drank more than two liters. She was no longer Mrs. R., but rather a malevolent, insidious witch with a colored mask.

...

The wide use of LSD as a hallucinogenic drug began in earnest in the 1960s when several counterculture figures (such as Timothy Leary, Ken Kesey, and Aldous Huxley) publicly touted the beneficial uses of LSD as a recreational drug. Eventually, and because of the extreme negative reactions in some individuals after taking LSD, the manufacture, sale, possession and use of the substance was made illegal in the United States in 1969. It is now listed as a Schedule I drug with no currently accepted medical use and a high potential for abuse.

For a more complete story of LSD as well as ergot alkaloids more generally, the reader is referred to two books by Albert Hofmann, both translated from the German:

*LSD: My Problem Child* (2009)

*Ergot Alkaloids, History, Chemistry, and Therapeutic Uses* (2023)

A short chapter in this latter text is entitled “On the history of ergot and its active substances,” and provides several historical instances where abductive reasoning played a role in the study of the “glorious chemical mess” that ergot represented. The first quote given below concerns who made the first connections between ergotism and the rye fungus and put to rest any claims that ergotism was some type of infectious disease. The second quote is about a possible relation between having a Vitamin A deficiency and a propensity to show symptoms of ergotism:

Ergot as a cause of ergotism was first recognized by Thuillier, personal physician to the Duke of Sully, on the occasion of an epidemic in Sologne (1630) and confirmed by feeding experiments on poultry. Sologne, south of the Loire near Orleans, was for centuries a notorious focus of gangrenous ergotism.

...

In this context, reference should be made to a study by E. Melenby showing that in the case of vitamin A deficiency, the susceptibility to ergotism is greater. With the general improvement of the nutritional situation, with the improvement of agriculture, and after the realization, obtained in the 17th century, that bread containing ergot was the cause of ergotism, the frequency and magnitude of ergot epidemics decreased steadily.

This short chapter will end with another discovery of Henry Dale

besides his identification and naming of the oxytocin hormone. Dale received the Nobel Prize in 1936 jointly with Otto Loewi “for their discoveries relating to the chemical transmission of nerve impulses.” Dale found in 1914 that “acetylcholine generated stimuli in part of the nervous system ... which has a dampening effect on heart activity and other functions.” In an article published in the journal *Diabetes* in 1954, Dale reminisced about the discovery of acetylcholine in a batch of ergot extract he was asked to test for possible clinical use. Note the “surprising” observations about the cat that was (again) being used as an animal model and the resulting abductive conjecture about nerve impulse transmission:

Then, about 1913, I was interrupted in the course of some other work which interested me. I was working then in a laboratory supported by industry, the Wellcome Laboratories, and I was interrupted by the arrival of an extract of ergot from the factory, with the request that I would test it, to see if it was suitable for clinical use. I thought this a nuisance, but I knew by experience that, if I postponed action, it would only make it worse, that I should get a series of reminders and things would pile up. So I said to my technician, “Bring along a cat and I’ll do this at once.” The cat was anesthetized and arrangements made for recording its arterial blood pressure in the conventional way, and I injected the customary dose of one cubic centimeter of this extract in the vein. And the cat’s heart stopped dead. I thought, “Oh, clumsy fellow, you’ve injected a bubble of air into the circulation, and it’s got into the coronary arteries, and that’s that.” I was turning away, to hang up my laboratory coat in disgust, and thinking, “I shall have to do another one now” when, out of the corner of my eye, I saw that the cat’s heart had begun to beat again; and, presently, the blood pressure was completely restored. I thought that I might as well try it again; so I gave another cubic centimeter, and exactly the same

thing happened again. Then I began to take notice. I thought that I'd never seen an effect quite like this before, with an ergot extract, or any other. I had better see what this extract would do to other sorts of organs; and I tested it in the usual sort of routine, on isolated strips of rabbit's intestine, perfused frogs' hearts, and so on; and presently there began to be built up the picture of a general parasympathomimetic action. Then it occurred to me that ergot was a fungus, and after all, muscarine, the classical example of a substance having that sort of action, came from a fungus. So I called my young friend, Ewins, who was my chemical colleague at the time, and I said, "Ewins, I'm going to condemn that batch of ergot anyhow. Nobody could conscientiously allow it to go for human treatment; but we'll keep it for research. You go ahead and see if you can get anything like muscarine out of it." Presently Ewins got a pinch of platinum salt, a few milligrams, of the active thing. It had the action which I had noted, but it was a very much more evanescent [disappearing] action than that of muscarine; and I began to suspect that it couldn't be muscarine itself, and that idea was accentuated by some other experiments. I dissolved some of it, freed from the platinum salt, in Ringer's solution, and perfused a frog's heart with varying dilutions on a warm day; and in a few hours the activity began to diminish and finally disappeared. I went down to Ewins and said, "Look here, that's a very unstable thing; in a weakly alkaline solution it just vanishes."

Ewins said, "Sounds like an unstable ester of some sort, doesn't it."

I said, "It does"

He said, "We'll never identify it. We've only got those few milligrams, and we can't do anything with that amount; so we'll just have to leave it there."

And then, as I was getting into bed that night, suddenly, from some lower subconscious layer, there whirled up into my consciousness the memory of Reid Hunt and the acetic ester of choline. So I went down to the laboratory the next morning rather earlier than



usual, from eagerness; and I caught Ewins and said, “Ewins, I wish you would get some choline and acetylate it for me. Let’s have some acetyl-choline.

...

## Chapter 3

# Two Medically Important Drugs Derived From Plant Sources Native to South America (Nineteenth Century)

Discovery consists of seeing what everyone has seen and thinking what nobody has thought.

— Albert Szent-Györgyi (1893–1986)

In discussions of plant-derived drugs having specific medicinal effects, there is usually a common theme present in the many discovery narratives about the first identification of a particular plant being the source of some medically relevant substance. That common element is one where the initial drug/plant connections have long been lost to history. Instead, we are left with observations about more contemporary indigenous medical practice where a plant has already been in use for some time. Thus, any abductive reasoning basis for identifying a plant-based source for a substance or drug usually rests with secondary European-based or otherwise gentrified individuals observing a set of “surprising” indigenous or folk practices. This leads to conjectures as to which plants contain medically relevant substances that alleviate or create various identifiable effects in ani-

mals and humans. Typically, there is an ensuing process of isolating the medically active substance in the plant. A later stage might even then seek to synthesize chemically the isolated compound and remove a dependence on any initial plant source.

The first drug to be discussed is the plant alkaloid of cocaine as contained in the leaves of the coca shrub native to the Andean mountain regions of South America. In these particular areas and long before the formation of the Incan Empire, coca leaves had been chewed for thousands of years as a way of increasing endurance and stamina, particularly at high altitudes, and to alleviate hunger and thirst and to induce more generally a feeling of well-being. But it wasn't until the overthrow of the Incan Empire by the Spanish conquistadors led by Francisco Pizarro (1478–1541) in the early Sixteenth Century that the coca plant became known to Europeans. One of the earliest accounts of the practice of chewing coca leaf was provided by the eponymous Amerigo Vespucci (1454–1512) in a letter to a friend that read in part:<sup>1</sup>

They all had their cheeks swollen out with a green herb inside, which they were constantly chewing like beasts, so that they could scarcely utter speech; and each one had [suspended] upon his neck, two dried gourds, one of which was full of that herb which they kept in their mouths, and the other [full] of a white flour, which looked like powdered chalk, and from time to time, with a small stick which they kept moistening in their mouths, they dipped it into the flour and then put it into their mouths in both cheeks, thus mixing with flour the herb which they had in their mouths; and this they did very frequently.

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<sup>1</sup>This passage is given in the book, *Coca Wine*, by Aymon de Lestrangé (2016).

The active substance contained in the coca leaf was first isolated by several German chemists in the middle 1850s, most notably by Albert Nieman (1834–1861) for his doctoral thesis in 1860 at the University of Göttingen. Besides naming the coca plant alkaloid “cocaine,” Nieman developed an improved purification process for extracting it from coca leaves. Several pharmaceutical companies soon thereafter began producing small quantities of the white cocaine powder for sale. One such American concern was Park, Davis & Company located in Detroit, Michigan. The owner, George Davis, published a self-serving in-house medical journal called the *Therapeutic Gazette* that included many articles touting the positive effects of cocaine, such as it being a possible cure for morphine and alcohol addiction. A second German pharmaceutical firm that further developed Nieman’s extraction method was Merck of Darmstadt. This small company supplied much of the cocaine that was experimented with in Europe during the 1880s and later.

The two individuals who most spurred the demand for cocaine from the 1880s onward were Sigmund Freud then working as an aspiring doctor at the Vienna Krankenhaus (General Hospital), and a young ophthalmology colleague, Karl Köller. As an impoverished young medical practitioner hoping to make a mark in his profession, Freud chose to write about the use of cocaine in the form of a literature review that also included several first-hand accounts of how cocaine affected him personally. In part of a letter given below that Freud wrote to his fiancée, Martha Bernays, on April 21, 1884, he discusses his hopes for the paper he was then working on; it was published in July of 1884 with the title of *Über Coca* (On Coca):<sup>2</sup>

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<sup>2</sup>In his *A Brief History of Cocaine* (Second Edition, 2006), Steven Karch comments on

I am also toying with a project and a hope which I will tell you about; perhaps nothing will come of this, either. It is a therapeutic experiment. I have been reading about cocaine, the effective ingredient of coca leaves, which some Indian tribes chew in order to make themselves resistant to privation and fatigue. A German has tested this stuff on soldiers and reported that it has really rendered them strong and capable of endurance. I have now ordered some of it and for obvious reasons am going to try it out ... particularly in the awful condition following withdrawal of morphine (as in the case of Dr. Fleischl). There may be any number of people experimenting on it already; perhaps it won't work. But I am certainly going to try it and, as you know, if one tries something often enough and goes on wanting it, one day it may succeed.

Freud continued his interests in cocaine until the late 1890s, after which he came to the realization that cocaine was itself addictive, and could not, for example, serve as a cure for a morphine addiction. The latter conclusion was unfortunately forced on Freud through the untimely death of a close friend, Ernst von Fleischl-Marxow, mentioned in his letter to Martha Bernays. He had developed a debilitating morphine habit after a botched thumb amputation.

Freud's young ophthalmology colleague, Karl Köller (1857–1944), had been on the search for an anesthetic that would be suitable for operations on the eye. In light of Freud's paper and through some "surprising" animal experimentation with frogs and guinea pigs and

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this first Freud publication as follows (p. 58): If it was published today, Freud's paper would be described as an editorial review paper: a paper describing the research of others, weighing its importance, and making recommendations for treatment based on the reported studies. But, Freud's paper was not based on placebo-controlled clinical trials, it was based upon unsubstantiated and anecdotal material, actually, paid advertisements. A paper like Freud's would never be published today, because no reputable modern journal would accept a review paper written by a physician with no experience in the field being reviewed.

eventually on himself and a colleague, Köller abductively conjectured that cocaine was the perfect type of local eye anesthetic he had been looking for. As he wrote a little while later:

... in that moment it flashed upon me that I was carrying in my pocket the local anesthetic for which I had searched for some years earlier. I went straight to the laboratory, asked the assistant for a guinea pig for the experiment, made a solution of cocaine from the powder which I carried in my pocketbook, and instilled this into the eye of the animal.

In September of 1884, a close colleague of Köller, Joseph Brettauer of Trieste, read his paper at the Heidelberg Ophthalmological Society and actually performed a demonstration of the local anesthetic effect of cocaine using a patient from the eye clinic. An American doctor in attendance named Henry Noyes mailed an account of this presentation to the *New York Medical Record*, which was published in early October of 1884. When he himself had sufficient time and funds available for travel, Köller followed closely with his own presentation in October at the Viennese Medical Society and carried out several subsequent demonstrations of cocaine's local anesthetic effects during actual eye surgery. The availability of an effective local anesthetic for the eye created an immediate international sensation and prompted a surge in demand for cocaine from those few companies then producing the drug.

One of the first Americans to read the summary Noyes report and to experiment with cocaine was William Halsted (1852–1922), then a young surgeon working on the East Coast in the area of New York City. Within a week after reading about Köller's discovery, Halsted and his colleagues were experimenting on themselves and others with

cocaine as a more general local anesthetic that extended much beyond any use with the eye. Halsted observed that when injected directly into a nerve, cocaine had the ability to block the perception of pain in that area – the classic meaning of a nerve-blocking agent. Unfortunately, given the continued self-experimentation engaged in by Halsted, he developed a debilitating and life-long addiction to both cocaine and morphine. For an engrossing account of the lives of both Freud and Halsted under the influence of cocaine, the reader is referred to Howard Markel’s well-received book: *An Anatomy of Addiction: Sigmund Freud, William Halsted, and the Miracle Drug Cocaine* (2011).

There are a number of salient cultural connections between the use of coca leaves and/or cocaine that were present in the latter part of the Nineteenth Century. One that preceded and spurred the development of the soft drink *Coca-Cola*, patented in 1887, was the introduction by Angelo Mariani (1838–1914) of coca wine in 1863. This wine, called *Vin Mariani*, was an extremely popular *fin de siècle* beverage endorsed by none other than the Pope as well as by many famous entertainers of the era. The story of *Vin Mariani* is told in the delightful book by Aymon de Lestrangé, *Coca Wine: Angelo Mariani’s Miraculous Elixir and the Birth of Modern Advertising* (2016).

A second prominent literary usage of cocaine at about the same time that *Vin Mariani* was popular is in the writings of Arthur Conan Doyle and his fictional detective, Sherlock Holmes. As one example among many others that could be given, the following is the introduction to the second Sherlock Holmes novel, *The Sign of the*

*Four*, first published in 1890:

Sherlock Holmes took his bottle from the corner of the mantel-piece and his hypodermic syringe from its neat morocco case. With his long, white, nervous fingers he adjusted the delicate needle, and rolled back his left shirt-cuff. For some little time his eyes rested thoughtfully upon the sinewy forearm and wrist all dotted and scarred with innumerable puncture-marks. Finally he thrust the sharp point home, pressed down the tiny piston, and sank back into the velvet-lined arm-chair with a long sigh of satisfaction.

Three times a day for many months I had witnessed this performance, but custom had not reconciled my mind to it. On the contrary, from day to day I had become more irritable at the sight, and my conscience swelled nightly within me at the thought that I had lacked the courage to protest. Again and again I had registered a vow that I should deliver my soul upon the subject, but there was that in the cool, nonchalant air of my companion which made him the last man with whom one would care to take anything approaching to a liberty. His great powers, his masterly manner, and the experience which I had had of his many extraordinary qualities, all made me diffident and backward in crossing him.

Yet upon that afternoon, whether it was the Beaune which I had taken with my lunch, or the additional exasperation produced by the extreme deliberation of his manner, I suddenly felt that I could hold out no longer.

“Which is it to-day?” I asked, — “morphine or cocaine?”

He raised his eyes languidly from the old black-letter volume which he had opened. “It is cocaine,” he said, — “a seven-per-cent solution. Would you care to try it?”

“No, indeed,” I answered, brusquely. “My constitution has not got over the Afghan campaign yet. I cannot afford to throw any extra strain upon it.”

He smiled at my vehemence. “Perhaps you are right, Watson,” he said. “I suppose that its influence is physically a bad one. I



find it, however, so transcendently stimulating and clarifying to the mind that its secondary action is a matter of small moment.”

\* \* \*

The second drug derived from a plant source to be discussed here is the antimalarial of quinine obtained from the bark of the Cinchona tree, which was native to the same Andean regions of South America where coca leaf had been chewed for thousands of years. Again, it was a common indigenous practice before the Spanish arrived in the 1500s to cure shivering and chills by drinking brews made from the bark of this Peruvian tree. The plant alkaloid of quinine acted as a muscle relaxant and palliative for the relief of shivering and associated chills. It was the Jesuit brother, Agostino Salumbrino (1561–1642), an apothecary living in Lima, who supposedly first observed the Quechua Indians in Ecuador using the powdered “fever bark” of the Cinchona tree to reduce the shaking caused by severe chills.

The term “ague” refers to any intermittent fever, such as that produced by malaria, which is marked by outbreaks of chills, fever, and sweating that reoccur at regular intervals. These cycles of fever may be termed quotidian (daily), tertian (every second day), or quartan (every third day). The initial source of the abductive conjecture about Cinchona bark being a general curative for ague remains unclear although there are several legends about how this happened. One that is often repeated involved Lady Chinchón, the wife of the Viceroy of Peru, who was cured of malaria by an infusion using the

powdered bark (Jesuits' Powder) from the Cinchona tree. The name of "Chinchona" was given by the Swedish taxonomist Carl Linnaeus, and was mistakenly formed by dropping an "h" from the Countess's name. In this apocryphal legend, the Countess is said to have brought the bark back to Europe after she herself had been cured. In actuality, however, Lady Chichón died in South America and never returned to Europe. What we do know is that this Peruvian bark was brought to Europe in the early 1630s by Jesuit missionaries, among them the explorer Bernabé de Cobo (1582–1657). The abductive conjecture that the alkaloid of quinine could actually cure and/or prevent bouts of malaria was a fortuitous result of the bark being able to alleviate the same general type of chills and fever that typically accompanied the disease.

Jesuits' Powder was promoted heavily by Cardinal John de Lugo for use on Roman fever (malaria) that was endemic to the infested marshland surrounding Rome called the Roman Campagna. Because Jesuits' Powder was putatively from a Catholic source, it was viewed with great suspicion in the Protestant England of the middle Seventeenth Century. Legend has it, for example, that the Great Defender, Oliver Cromwell, died in 1658 from the (tertian) ague rather than seek help from any Catholic inspired Jesuits' Powder. It eventually found its way to England in the 1660s through a (quack) physician named Robert Talbor (1642–1681) who incorporated Jesuits' Powder in a proprietary medicine he developed as a cure for ague.

Because his secret cure for ague worked, Robert Talbor was appointed court physician to the English King Charles II in 1678. Just one year later, Talbor was able to cure the king himself of a bout

of malaria. Talbor went on to cure the French Louis XIV's son and heir, and made a lucrative deal with the king to reveal the recipe for his potion after his death. The brew developed by Talbor consisted in its essentials of an ounce of bark mixed with two pints of red wine, which was to be given in measured doses of eight or nine spoonfuls over a short period of time. The inscription for the English translation of Talbor's secret cure read as follows (all spellings in the sections below are "in context"):

The English remedy, or, Talbor's wonderful secret for cureing of agues and feavers sold by the author Sir Robert Talbor to the Most Christian King, and since his death ordered by His Majesty to be published in French for the benefit of his subjects; and now translated into English for publick good.

The section devoted to actually developing the infusion was as follows:

The first infusion of Quinquina, or the Jesuits Powder making a part of the English Remedy.

Take a pound of the best bark of Quinquina beaten to a subtil powder and searced, besprinkle it interchangably for the space of a day or two with the decoction of Anis and the juice of Parsley, then put the powder into an Earthen Pitcher holding about fifteen or sixteen quarts, pour upon it gently and still stirring the matter, as much good Claret Wine as the Vessel will hold, and having afterward stopt it well, let your mixture infuse for the space of eight days without setting it near the fire, but not forgetting to stir it two or three times a day with a stick or instrument fit to stir the bottom, afterward having poured off your liquor, through a close strainer, put it into glass bottles, which being well stopt and placed in a dry place not too Airy, will preserve it in full force and virtue two or three months and more.

In 1820, the French chemists Pierre Pelletier and Joseph Caventou separated the alkaloid of quinine from powdered “fever tree” bark. This allowed for the creation of standardized doses for the active ingredient of quinine, and, in turn, for the first successful use of a chemical compound to treat an infectious disease. In 1918, quinine was successfully synthesized but the process proved very elaborate and expensive. Because of this, modern production of quinine still relies on extraction directly from the bark of the Cinchona tree.

The word “malaria” comes from the Medieval Italian “mal aria” meaning “bad air,” and was first used in an English scientific publication in 1827. In 1880 the causative malaria *Plasmodium* parasite was discovered in the red blood cells of patients with malaria by the French physician Charles Laveran (1845–1922) working at a military hospital in Algeria. As discussed in the chapter on Patrick Manson in the larger companion volume, the transmittal by the bite of the female *Anopheles* mosquito was explicated by Ronald Ross in the late 1890s, for which he received the Nobel Prize in 1902. Even today, malaria remains the single most prevalent life-threatening infectious disease in the world. It has played major roles in the various world wars waged in the past several centuries. As discussed in other chapters, malaria has been central to the search for drugs of more general medical value as in Paul Ehrlich’s discovery of the antimalarial properties of methylene blue, or to the use of induced malarial fever as a cure for late-stage neurosyphilitic individuals invented by Julius Wagner-Jauregg in the early Twentieth Century.

There has also been a significant amount of commercial and military intrigue over the last several hundred years involving the identi-

fication and growing of high-yielding Cinchona tree seeds in regions away from where they were native. These sagas include, for example, the Dutch monopoly in the late 1920s on quinine obtained from the extensive plantations in their Indonesian colonies. There are several sources listed below that discuss in detail the discovery of the medical uses for the bark of the Cinchona tree and its quinine alkaloid, as well as for the political aspects of quinine discovery and use:

Marie Louise Duran-Reynals (1946). *The Fever Bark Tree: The Pageant of Quinine*. Doubleday & Company, Garden City, New York.

Norman Taylor (1965). *Plant Drugs that Changed the World*. Dodd, Mead, & Company, New York.

Mark Honigsbaum (2001). *The Fever Trail: In Search of the Cure for Malaria*. Farrar, Straus and Giroux, New York.

Fiammetta Rocco (2003). *Quinine: Malaria and the Quest for a Cure that Changed the World*. HarperCollins Publishers, New York.

Henry Hobhouse (2005). *Seeds of Change: Six Plants that Transformed Mankind*. Counterpoint, Berkeley, California.

## Chapter 4

# The Development of Anesthesia (1844)

To the woman he said,

“I will make your pains in childbearing very severe; with painful labor you will give birth to children. Your desire will be for your husband, and he will rule over you.”

— Genesis 3:16

Nitrous oxide, known more familiarly as “laughing gas,” was discovered in 1772 by the English chemist, Joseph Priestly (1733–1804), using a simple process of heating iron filings dampened by nitric acid. Under the view that such “factitious airs” might prove useful in treating respiratory diseases such as tuberculosis, a Pneumatic Institute was opened at Bristol in 1798 with Humphry Davy (1778–1804) acting as superintendent. Davy and his friends were soon engaged in inhaling a variety of such “factitious” gases to assess their effects. Because of the pleasant and exhilarating result that nitrous oxide produced, it was a particular favorite among Davy’s group of inhaling colleagues.

Davy was the person responsible for attaching the “laughing gas” sobriquet to nitrous oxide. He also made a prophetic remark about

the possible use of nitrous oxide as an anesthetic although neither he nor anyone else at the time followed up on this “surprising observation.” The relevant comment below is taken from his publication “Researches, Chemical and Philosophical, Chiefly Concerning Nitrous Oxide and Its Respiration” —

... as nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusing of blood takes place.

During the first half of the Nineteenth Century, nitrous oxide enjoyed widespread popularity in various types of “laughing gas” parties centered primarily around college-age individuals and large public exhibitions. One such spectacle given on the evening of December 10, 1844, was to signal the birth of nitrous oxide as a surgical anesthetic useful first in dental practice and the painless extraction of teeth. The exhibition was organized by Gardner Colton in Hartford, Connecticut, and was staged in the town’s large Union Hall. Part of a newspaper announcement follows, taken from the *Hartford Courant* on December 10, 1844:

A GRAND EXHIBITION of the effects produced by inhaling NITROUS OXIDE, EXHILARATING or LAUGHING GAS! will be given at UNION HALL, THIS (Tuesday) EVENING, Dec. 10th, 1844.

FORTY GALLONS OF GAS will be prepared and administered to all in the audience who desire to inhale it.

TWELVE YOUNG MEN have volunteered to inhale the Gas, to commence the entertainment.

EIGHT STRONG MEN are engaged to occupy the front seats, to protect those under the influence of the Gas from injuring them-

selves or others. This course is adopted that no apprehension of danger may be entertained. Probably no one will attempt to fight.

THE EFFECT of the GAS is to make those who inhale it either Laugh, Sing, Dance, Speak, or Fight, &c., &c., according to the leading trait of their character. They seem to regain consciousness enough to not say or do that which they would have occasion to regret.

N.B. The Gas will be administered only to gentlemen of the first respectability. The object is to make the entertainment in every respect a genteel affair.

...

Two individuals present at the Exhibition are central to our story — Samuel Cooley, a local drug-store clerk, and Horace Wells, a well-known dentist in the Hartford area. The “surprising observation” and ensuing abductive conjecture made by Wells were about the injuries suffered by Cooley that evening and his apparent inability to feel them. This circumstance led directly to the first use of an anesthetic in surgical dental practice. A short summary of this episode is given below as reported in an article appearing in the *Yale Journal of Biology and Medicine* (May, 1933) by Henry Wood Erving, entitled “The Discoverer of Anaesthesia: Dr. Horace Wells of Hartford”:

On the evening of December 10, Dr. Wells was present, searchingly watching every movement of those engaged, with the most fervent interest. At length “Sam” Cooley took the gas and proved to be an interesting subject. He careered about the stage in an extraordinary manner when suddenly he espied in the audience an imaginary enemy and sprung over the ropes and after him. The innocent spectator, frightened out of his seven wits, summarily abandoned his seat and fled, running like a deer around the hall with Cooley in hot pursuit, the audience on its feet applauding in delight. The terrified victim finally dodged, vaulted over a settee



and rushed down an aisle, Cooley a close second. Half way to the front the pursuer came to himself, looked about foolishly, and amid shouts of laughter and applause slid into his seat near to Dr. Wells. Presently he was seen to roll up his trousers and gaze in a puzzled sort of way at an excoriated and bloody leg.

“How did that happen, Sam?” exclaimed the doctor.

“I’ve no idea.” Cooley replied, “it’s the first I knew of it.”

He had scraped his shin on the sharp back of the settee when he sprung over it.

“Didn’t you feel it at all?” exclaimed Dr. Wells.

“Not at all,” said Sam, “I just now felt a little smarting on my shin and looked.” And there and then was the great discovery made!

Dr. Wells was tremendously excited, and on the very next morning, Dr. Riggs in his office [a fellow dentist with Wells], with Dr. Colton giving the gas – a larger quantity than anyone had ever before inhaled – extracted, after insensibility had been effected, a molar from Dr. Wells’ jaw, with no pain whatever on the part of the patient. A great event had taken place — it was a momentous occasion.

The further development of anesthesia after this first demonstration by Wells constitutes a tangled story involving other proposed anesthetics, such as ether and chloroform, as well as several other individuals who for whatever reason claimed priority in the first use of anesthesia (see, in particular, the references to William Morton (1819–1868), Charles Jackson (1805–1880), and Crawford Long (1815–1878)). Because this complete story would take us far away from an emphasis on the “surprising observation” made by Wells and the subsequent abductive conjecture that nitrous oxide could serve as a surgical anesthetic, we refer the reader to several sources that fill in the whole history:

Victor Robinson (1946). *Victory Over Pain*. Henry Schuman, Inc., New York.

Julie M. Fenster (2001). *Ether Day: The Strange Tale of America's Greatest Medical Discovery and the Haunted Men Who Made It*. HarperCollins Publishers, New York.

Stephanie J. Snow (2008). *Blessed Days of Anaesthesia: How Anaesthetics Changed the World*. Oxford University Press, New York.

## Chapter 5

# Paul Ehrlich and the Search for Medical “Magic Bullets” (1907)

The art of medicine consists of amusing the patient while nature cures the disease.

— Voltaire

The German discovery of the first “miracle” sulfa drug in the 1930s discussed in another vignette had its earlier beginnings in the work of Paul Ehrlich (1854–1915) and his methodical search for medical “magic bullets” (*Zauberkekugeln*) that would kill particular disease-causing microbes without harming a host body. The “magic bullet” concept comes from a German opera by Carl Maria von Weber in which a young hunter must hit an impossible target before he is allowed to marry his bride. In the case of Ehrlich, his most significant magic bullet was in the 1909 chemical construction of the arsenic-derived compound, Salvarsan, as a treatment for syphilis. This artificially produced substance marked the beginnings of chemotherapy and the fight against disease that proceeded through, first, a systematic search for chemically derived substances of possible medical usefulness, and second, a subsequent experimental evaluation of these constructed compounds against some specific type of malady present

in an appropriate animal model. To Ehrlich, chemotherapy meant the use of chemical substances, especially those produced synthetically, to destroy pathogenic organisms within the human body.

Partly through the influence of his older medically trained cousin, Karl Weigert (1845–1904), Ehrlich became deeply interested as a schoolboy in the process of staining microscopic tissue samples and more generally in how chemical substances became distributed and were active in the body in accordance with their varying affinities for different tissue types. His doctoral thesis in 1878 to the medical faculty of the University of Leipzig contained a set of “surprising observations” regarding the selective uptake and staining of different tissue elements using a variety of dyes. In addition, Ehrlich’s thesis presented at least implicitly the abductive conjecture that some differential stainings might result in histochemical reactions having therapeutic medical value. In other words, dyes were sought that might bond to a disease-causing organism within the body and bring along some type of poison to kill the microbe. It is this latter conjecture that Ehrlich would first study with the dye of methylene blue.

In the 1880s Ehrlich carried out several experimental studies with methylene blue. One such investigation was concerned with the dye having a selective affinity for nerve cells and nerve-fiber endings, and in its possible applications as a (weak) analgesic. A second application was in the dye’s selective staining of the malaria parasite and in its use as a possible antimalarial. In this latter context and although the dye proved somewhat therapeutic, it was not as good as the much older quinine cure. Nonetheless, methylene blue continued to be used as an antimalarial preventive up through the second World

War although it was not well-liked by sailors who commented: “Even at the loo, we see, we pee, navy blue.”

From as far back as 2000 B.C., arsenic and inorganic arsenical compounds have been used as both medicines and poisons. In fact, during the nineteenth century, arsenicals such as Fowler’s solution which was composed of one percent potassium arsenite, became preeminent medicines against a variety of diseases irrespective of their effectiveness. In the late 1850s, Antoine Béchamp (1818–1908) in France synthesized the first organic arsenical substance that he named Atoxyl. During the early years of the twentieth century, reports of the successful clinical use of Atoxyl in animals against *trypanosomiasis* (“sleeping sickness”) appeared in Britain. Unfortunately, a human clinical Atoxyl trial in German East Africa carried out by Robert Koch proved the arsenical too toxic for human use — some two percent of all trial patients were actually blinded through an atrophy of the optic nerve.

Paul Ehrlich became director in 1906 of the George Speyer House in Frankfurt which had been set up as a private research foundation affiliated with Ehrlich’s other position as director of the Institute of Experimental Therapy, also located in Frankfurt. It was here that Ehrlich along with his chemist Alfred Bertheim proceeded to synthesize various Atoxyl derivatives that were then experimentally tested by the Japanese bacteriologist Sahachiro Hata against the newly discovered microorganism that caused syphilis. The rabbit was adopted as a suitable animal model for conducting the initial clinical trials because of the rabbit’s susceptibility to syphilitic infection.

The Atoxyl derivative synthesized in 1907, labeled “606” and called

arsphenamine, proved effective against the spirochete causing syphilis.<sup>1</sup> It was eventually mass-marketed by the company Farbwerke Hoechst under the trade name of Salvarsan (“the arsenic that saves”). It soon became the most widely prescribed drug in the world. Salvarsan epitomized Ehrlich’s concept of a “magic bullet” for the treatment of a particular disease. It was also the world’s first synthetic chemotherapeutic agent and the paradigmatic example of industrial drug discovery that proceeded through the use of subsequent clinical trials for all the many derivatives that might be produced from a single initial compound. For this process, Ehrlich can rightly be considered the father of modern drug development.

\* \* \*

The story of Salvarsan’s development is told in a well-received 1940 American biographical film starring Edward G. Robinson as Paul Ehrlich. Parts of a Wikipedia article summarizing the plot and reception for the film entitled *Dr. Ehrlich’s Magic Bullet* is given below. It should be noted that the relationship between Ehrlich and Emil von Behring was not nearly as cordial as indicated in this summary. The difficulty resided in von Behring’s disregard for Ehrlich’s central role in developing a viable diphtheria antitoxin for which von Behring received considerable financial reward in addition to the very first Nobel prize in Physiology or Medicine (1901).

Paul Ehrlich is a physician working in a German hospital. He is dismissed for his constant disregard for hospital rules, which are bound by bureaucratic red tape. The reason for his conflict is his

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<sup>1</sup>The number “606” refers to a 6th version of a 6th derivative compound.

steadily rising interest in research for selective color staining, the marking of cells and microorganisms using certain dyes and marking agents which have a certain ‘affinity’ for their target and nothing else. Emil von Behring, whom Dr. Ehrlich meets and befriends while experimenting with his staining techniques, is impressed with Dr. Ehrlich’s staining methods and refers to it as ‘specific staining,’ adding that this optical microscopy diagnostic technique is one of the greatest achievements in science.

After attending a medical presentation of the eminent Dr. Robert Koch demonstrating that tuberculosis is a bacterial disease, Ehrlich is able to obtain a sample of the isolated bacterium. After an intense time of research and experimentation in his own lab, paired with a portion of luck and thanks to the empathy of his wife, he is able to develop a viable staining process for the microbe. This result is honored by Koch and medical circles as another highly valuable contribution to diagnostics.<sup>2</sup>

During his work Dr. Ehrlich is infected with tuberculosis, then an often-deadly, incurable disease. To recover, Ehrlich travels with his wife Hedwig to the hot dry climate of Egypt. There he starts to discover the properties of immunity. This discovery helps Ehrlich and colleague Dr. von Behring to fight a diphtheria epidemic that is killing off many children in the country. The two doctors are rewarded for their efforts.

Ehrlich concentrates on work to create “magic bullets” – chemicals injected into the blood to fight various diseases, thus pioneering antibiotic chemotherapy for infectious diseases. Ehrlich’s labora-

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<sup>2</sup>The manner in which Ehrlich was able to develop a viable staining method for the tuberculosis (TB) bacillus can be phrased as an example of (propitious) abductive reasoning. In trying to develop an appropriate dye to clearly stain the TB microbe, Ehrlich placed what he thought were unsuccessfully stained slides on a cold heater in his lab. The heater was inadvertently turned on by the housemaid without first removing the slides. When Ehrlich reoccupied his lab, he noticed the “surprising” observation that the warmed slides now showed clearly the rods of the TB bacillus. The ensuing abductive conjecture that would prove invaluable even to the present was that heat was needed at times to “fix” a stain for a particular microbe to appear clearly.

tory has the help of a number of scientists like Sahachiro Hata. The medical board, headed by Dr. Hans Wolfert, believes much of Ehrlich's work is a waste of money and resources and fight[s] for a reduction, just as Ehrlich begins to work on a cure for syphilis. Ehrlich is financially backed by the widow of Jewish banker Georg Speyer, Franziska Speyer, and after 606 tries [sic] he finally discovers the remedy for the disease. This substance, first called "606", then Salvarsan, is now known as Arsphenamine.

The joy of discovery is short-lived, as 38 patients who receive the treatment die. Dr. Wolfert denounces the cure publicly and accuses Ehrlich of murdering those who died from the cure. As faith in the new cure starts to dwindle, Ehrlich is forced to sue Wolfert for libel and in the process exonerate 606. Dr. von Behring (who had earlier told Ehrlich to give up his pipe dreams of cures by chemicals), is called by the defense to denounce 606. Behring instead states that he believes that 606 is responsible for a 39th death: the death of syphilis itself. Ehrlich is exonerated, but the strain and stress from the trial are too much for his weakened body and he dies shortly thereafter, his final words being counsel to his assistants and colleagues on the risks involved in advancing medicine.

...

Warner Bros. Studios was concerned about *Dr. Ehrlich's Magic Bullet* because it was about a venereal disease, syphilis, and because Ehrlich was Jewish. This was before the U.S. entry into the Second World War. Warner Bros. did not want the movie to be political or seem to have a Jewish agenda since Germany was still a market for American films. However, Warner Bros. had already produced a series of medical biographical films during the 1930s, including ... *The Story of Louis Pasteur* (1935) and *The White Angel* (1936) about Florence Nightingale. In addition, U.S. Surgeon General Thomas Parran Jr. had in late 1936 begun a syphilis control campaign to get the public to consider it to be a medical condition and not a moral failure, suggesting that a film on Ehrlich's life would be acceptable.

Ehrlich was one of the greatest Jewish doctors, and in 1908 his



work on immunity won a Nobel Prize. However, the Nazi regime in Germany had systematically expunged all memory of Ehrlich from public buildings and street signs and censored books referring to him. The Second World War had already begun but the United States was not yet directly involved. Jack Warner, like other Hollywood moguls, was wary of criticism of pursuing any supposedly “Jewish” agenda on the screen. A memorandum circulated by the studio bosses stated with regard to the forthcoming Ehrlich movie: “It would be a mistake to make a political propaganda picture out of a biography which could stand on its own feet.” So the words “Jew” and “Jewish” went entirely unmentioned in the film. Anti-Semitism in Ehrlich’s life was no more than hinted at, and then only once or twice. In addition, the original version of the deathbed scene was changed so that Ehrlich no longer would refer to the Pentateuch (books of Moses in the Bible). Nevertheless, the film’s story writer Norman Burnside declared “There isn’t a man or woman alive who isn’t afraid of syphilis, and let them know that ... Ehrlich tamed the scourge. And maybe they can persuade their hoodlum friends to keep their fists off Ehrlich’s coreligionists.”

One prohibited topic of the Motion Picture Production Code adopted in 1930 was “sex hygiene and venereal diseases” and after 1934 studios were required to submit films to the Production Code Administration for approval. Aware of the restrictions of the Code, Warner executives seriously considered not mentioning the word “syphilis” in the movie. However, Hal B. Wallis, Warner Bros. head of production, while advising caution, wrote to the PCA that “to make a dramatic picture of the life of Dr. Ehrlich and not include this discovery [the anti-syphilis drug Salvarsan] among his great achievements would be unfair to the record.” Following negotiations, the film received approval under the Production Code provided no scenes showing treatment of patients with syphilis were shown, and advertising of the film could not mention syphilis.

The movie’s title role star Edward G. Robinson, himself Jewish, was keenly aware of the increasingly desperate situation of the Jews

in Germany and Europe, and anxious for the opportunity to break out of the police and gangster roles in which he was in danger of being forever stereotyped. He met with Paul Ehrlich's daughter who had fled to the US and he corresponded with Ehrlich's widow, who was a refugee in Switzerland. "During the filming" Robinson later recalled with regard to his role as Ehrlich: "I kept to myself, studied the script, practiced gestures before the mirror, read about his life and times, studied pictures of the man, tried to put myself in his mental state, tried to be him."

## Chapter 6

# Four Brief Psychiatric Tales That Rely Implicitly On a Biological Basis for Mental Illness: (Electro)convulsive and Fever Therapy, Surgical Lobotomy, and Insulin Coma Induction (1920)

I'd rather have a bottle in front of me than a frontal lobotomy.

— Dorothy Parker (1893–1967)

Our first short psychiatric tale is about Julius Wagner-Jauregg (1857–1940), an Austrian physician and the first psychiatrist to win a Nobel Prize in Physiology or Medicine (1927). The prize citation reads: “for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica.” Dementia paralytica is a generally terminal brain condition characterized by progressive mental deterioration as typically seen in late-stage neurosyphilitic individuals. Fever therapy (also known as pyrotherapy) as produced by malarial inoculation was the first successful physical therapy developed in psychiatry. It was widely used as a heroic measure in

neurosyphilitic individuals prior to the development of penicillin in the 1940s, the first effective antibiotic against syphilis itself.

In 1883 during a medical residency at the First Psychiatry Clinic at the Asylum of Lower Austria, Wagner-Jauregg cared for a female patient in remission from her psychosis after contracting erysipelas, a streptococcal infection of the skin that typically presents with a high fever. This “surprising observation” piqued Wagner-Jauregg’s interest in the general relationship of fever to mental illness, and led to his abductive hypothesis about the curative power of fever, which was formalized in an article he wrote in 1887, entitled: “the effect of feverish diseases on psychoses.” Besides the evidence provided by this one patient with erysipelas, there were many more such cases, some even dating from the time of Hippocrates, of fever appearing to be curative for certain mental conditions. The typhoid epidemics that periodically ravaged asylums provided a particularly compelling set of observations for the conjecture that psychoses, defined by collections of symptoms affecting the mind and inducing some loss of contact with reality, could be treated through fever therapy. Because the syphilis spirochetes responsible for the many neurosyphilitics housed in the various asylums across Europe were heat sensitive, a plausible mechanism was even available to explain some of the remissions that occurred.

Initially, Wagner-Jauregg used injections of Koch’s tuberculin to stimulate a patient’s fever, and although somewhat successful, tuberculin eventually proved too toxic for general use and was abandoned by 1909. In 1917 a soldier with malaria returning from the First World War was admitted to the same hospital where Wagner-Jauregg

was in residence. In May of 1917 a 37-year-old neurosyphilitic male actor was transfused with blood from the soldier. After six recurring episodes of malaria-induced fever, the patient was “cured.” A subsequent treatment with quinine then eliminated the healing malaria parasite itself. After this first trial and several similar successful clinical demonstrations, malarial therapy became a staple of psychiatry practice for treating neurosyphilitics at least until the antibiotic penicillin became available in the middle 1940s. As noted earlier, this type of malariotherapy could be considered the first effective physical treatment for any form of mental illness.

Ladislav Meduna (1896–1964) was a Hungarian neuropsychiatrist who in the middle 1930s introduced convulsions as a treatment for various psychoses including schizophrenia. The “surprising” post-mortem observation that the brains of patients who died with epilepsy had more brain glia (that is, more non-neuronal cells that do not produce electrical impulses) than did the brains of schizophrenics, led Meduna to the abductive conjecture that a lack of brain glia was a cause of schizophrenia. Further observation supported the notion that schizophrenia and epilepsy were somehow antagonistic diseases: the incidence of schizophrenia was low among hospitalized epileptic patients; also, a number of schizophrenic patients were relieved of their psychotic symptoms after they had developed seizures from infections or various forms of head trauma.

Based on the glia discrepancies between epileptics and schizophrenics, Meduna arrived at the treatment hypothesis that an induction of grand mal seizures in schizophrenic patients mimicking those seen naturally in epileptics would increase brain glia, which in turn would

relieve the symptoms of the mental illness. Meduna began with seizure induction produced chemically by first injecting camphor-in-oil intramuscularly. Later he moved to the intravenous use of pentyleneterozol (also known as metrazol or cardiazol). The first of Meduna's patients at a psychiatric hospital outside of Budapest were diagnosed as catatonic and generally unaware of their surroundings. At the time, catatonia was considered to be a form of schizophrenia, and as it so happened was very responsive to chemically induced seizures. These initial successes were soon recognized as the first effective therapy available for schizophrenia. This was also a conclusion that could be made irrespective of the truth of any dubious abductive conjecture about glia discrepancy on which the therapy was supposedly based.

The move from the use of drug-induced convulsions in the middle 1930s to electroconvulsive therapy (ECT) in the 1940s is usually attributed to the Italian neurologist, Ugo Cerletti (1877–1963), working at the University of Rome (La Sapienza). As the story is typically told, Cerletti was on his way home when he stopped by a butcher shop for a particular cut of meat that he wanted. He was told the cut of meat was available only at the slaughter house behind the shop. The technique Cerletti saw at the slaughterhouse for butchering cattle and pigs (the “surprising observations”) involved an electric shock to an animal's head. The induced seizures in the pigs and cattle made them fall down so that it was then relatively easy in this anesthetized state to slit their throats. Based on the Meduna view (and abductive conjecture) that seizures were essential in preventing schizophrenia, and that those individuals diagnosed with epilepsy were supposedly immune to the disorder, Cerletti reasoned that electric shock might

therefore be useful as a treatment for human schizophrenia.

Cerletti and several colleagues, such as Lucio Bini (1908–1964) continued extensive animal experimentation on pigs at the slaughter house and on dogs in their own animal laboratories in an attempt to perfect the induction of non-lethal seizures that had quicker onset and few apparent side effects. Finally, in 1938 they conducted a first human trial on a 39-year-old disorganized schizophrenic male found by police wandering around a train station in Rome. After eleven such treatments over the course of the patient’s hospital stay, his psychotic symptoms were successfully attenuated to the point that he could return to his wife and former job in the community. From that point on, ECT grew in popularity throughout the 1940s in both Europe and the United States.

By the early 1940s, convulsive therapy, whether drug-induced or done by electric shock, was in widespread use throughout the United States and Europe. In addition to these two forms of somatic intervention, a third insulin-induced coma therapy was also common. The use of insulin comas was discovered by Manfred Sakel (1900–1957) in the early 1930s working at a sanatorium in Berlin that specialized in drug addiction. As the story goes, a famous actress in residence who was both diabetic and addicted to morphine was given an accidental insulin overdose by Sakel that produced a mild coma. After recovery, the actress’s morphine craving subsided. A second supposedly accidental insulin overdose was given to a patient who was both a drug addict and psychotic. In this case after recovery, both the psychotic and addiction symptoms were lessened. Relying on these first two “surprising observations” and several others that Sakel purposely

carried out, this aductively generated therapy of insulin coma induction became fairly widespread both in Europe and the United States. One of the reasons for its success was relative safety – an insulin coma could be quickly relieved merely by the intravenous administration of glucose.

Our final psychiatric tale is about the use of a surgical leucotomy (better known as a lobotomy) defined by a neurosurgical intervention that involves severing some of the connections in the prefrontal cortex of the brain. Although such surgeries are rarely if ever performed today given the availability of alternative nonsurgical drug treatments for the same mental conditions that lobotomies were supposedly directed toward mitigating, it was widely practiced in Europe and the United States throughout the 1940s and 50s. Few of us of a certain age, for example, can escape the frightful images presented by the 1975 movie, *One Flew Over the Cuckoo's Nest*, based on the Ken Kesey novel of 1962. Here, the rebellious Randle McMurphy (played by Jack Nicholson) is “cured” through a lobotomy orchestrated by nurse Ratched (played by the recently deceased Louise Fletcher).

Credit for the first human lobotomy is typically given to the Portuguese neurologist Egas Moniz (1874–1955). As the story is usually told, Moniz attended the Second International Congress of Neurology held in London in August of 1935. During an extended session that Moniz attended, two Yale researchers, Carlyle Jacobson and John Fulton, presented experimental results involving two chimps, named Becky and Lucy, and their performances on short-term memory tasks after removal of a portion of their frontal lobes. Moniz was particularly intrigued by the dramatic changes after surgery in the



emotional states shown by the chimps. He was said to inquire directly of Fulton and Jacobson whether they thought that frontal lobe surgery could possibly relieve anxiety states and neuroses in humans as well. The answer was presumably positive based on Fulton's extensive work in the 1930s on primate frontal lobotomy and affective behavior generally.

In less than three months after hearing the Fulton-Jacobson report in London, Moniz directed his first leucotomy (lobotomy) in Lisbon in November of 1935. Because Moniz had a severe crippling condition in his hands caused by gout, the neurosurgeon Almeida Lima actually performed the first series of operations as supervised by Moniz. In the initial group of ten, absolute alcohol was injected to destroy parts of the frontal lobe. A technique developed later on was based on a leucotome, a needle-like instrument with a retractable wire that could be rotated to surgically separate and sever the white matter fibers present in the frontal lobes.

In the first set of twenty surgeries that Moniz supervised, he reported a total of seven "cures," seven "improvements," and six "unchanged" cases. Although he consistently understated complications and provided inadequate documentation and little patient follow-up, Moniz nevertheless confidently claimed in his early reports that "prefrontal leucotomy is a simple operation, always safe, which may prove to be an effective surgical treatment in certain areas of mental disorder." Moniz also argued that any behavioral and personality deterioration that might occur was far outweighed by the reduction in the debilitation caused by the original mental illness. The Nobel Prize in Physiology or Medicine was awarded to Moniz in 1949

with the following stated prize motivation: “for his discovery of the therapeutic value of leucotomy in certain psychoses.”

Although the “surprising observations” of the chimps’ behavior after receiving lobotomies that lead directly to Moniz conducting his first human surgeries, it was a specific dubious abductive conjecture that justified the explicit goal of severing the fibers present in the frontal lobes that made connections with the rest of the brain. A summary is provided below of Moniz’s reasoning that is taken from the 1986 book, *Great and Desperate Cures*, by Elliot Valenstein (p. 84):

Moniz’s argument for prefrontal leucotomy was based solely on a series of general, loosely connected, and essentially untestable statements. First, he asserted that the frontal lobes are the seat of man’s “psychic activity,” and that thoughts and ideas are somehow stored in the nerve-fiber connections between brain cells. Moniz then stated that all serious mental disorders are the result of “fixed” thoughts that interfere with normal mental life. Here he was apparently generalizing the concept of an *idée fixe*, which Pierre Janet considered to be the cause of hysteria, and applying it to all mental disturbances. Moniz argued that “fixed thoughts” are maintained by nerve pathways in the frontal lobes which have become pathologically “fixed” or “stabilized.” Effective therapy, according to Moniz, required the destruction of these abnormally “stabilized” pathways in the frontal lobe.

In the late 1930s the center of human psychosurgery shifted to the United States and to Walter Freeman (1895–1972), then head of the neurology department at George Washington University in Washington, D.C. By the early 1940s, Freeman and his surgical colleague,

James Watts, had performed some several hundred lobotomies with putatively 63% of patients improving after surgery, 23% unchanged, and 14% worse. These initial lobotomies done by Freeman-Watts differed from the original Moniz procedure which took small cores of the patient's frontal lobes. Instead, Freeman's strategy completely severed the connections between the frontal lobes and the thalamus.

In 1946 Freeman developed a new transorbital approach for performing a lobotomy where the patient's brain was accessed and operated on through eye sockets instead of drilling through the skull. This new approach allowed Freeman to perform a lobotomy without anesthesia by simply applying electroconvulsive therapy to induce a seizure and unconsciousness. A mallet was then used to tap an orbitoclast (a rod-shaped instrument resembling an ice-pick) through the orbital roof. The orbitoclast would then be swept laterally to obliterate the frontal lobe tissue connecting to the thalamus. Freeman was able to carry out the transorbital procedure in a simple office setting where patients could be anesthetized with a portable electroshock machine. In opposition to this office-like transorbital procedure, his long-time colleague, James Watts, separated himself from Freeman and quit their joint practice in 1950.

From 1950 onwards, Freeman barnstormed the country visiting mental institutions, performing lobotomies, and spreading his views and techniques to institutional staff. It is said that he traveled in a van named the "lobotomobile." As an estimate, Freeman performed well over 4,000 lobotomies during the course of his career including some 2,500 of the transorbital variety. Freeman gained widespread notoriety following a lobotomy performed on President

John F. Kennedy's sister, Rosemary Kennedy, which left her with severe mental and physical disabilities. This whole unfortunate story is told by Kate Clifford Larson in *Rosemary: The Hidden Kennedy Daughter* (2016).

In February of 1967, Freeman performed his last surgery on Helen Mortensen, a long-term patient receiving her third lobotomy. She died of a cerebral hemorrhage as did some one-hundred or so of Freeman's other patients over the years. After the death of Mortensen, Freeman's hospital and surgical privileges were finally revoked; he retired a short time later.<sup>1</sup>

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<sup>1</sup>Although there are many books that deal separately with the topics included in this short chapter, the excellent text by Edward Shorter covers them all and in some detail: *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac* (1997; John Wiley & Sons, New York).

## Chapter 7

# Insulin As a Means For Controlling Diabetes (1921)

Diabetes is no longer a death sentence.

— Frederick Banting (Nobel Laureate in 1923)

One of the most significant medical discoveries of the twentieth century was in the identification and development of insulin as a means for controlling diabetes. As might be expected from the various short narratives given thus far, the original impetus for such a major medical advance was made by a single individual recognizing the importance of a specific “surprising observation,” and who subsequently constructed an explanatory hypothesis that would account for it. In the case of insulin, Oskar Minkowski (1858–1931) was the one individual who initiated the research path that would eventually lead to the isolation and use of insulin as a mechanism for the control of diabetes.

Oskar Minkowski (1858–1931) was born in Lithuania, Russia, in January of 1858. Because of antisemitic Tzarist measures then being imposed, Oskar’s family moved to Königsberg, Prussia, in 1872. Minkowski completed his medical studies at the University of Königsberg

in 1881 under Bernhard Naunyn (1839–1935), and eventually moved with his mentor Naunyn to the University of Strasbourg. Minkowski stayed at Strasbourg through 1904 until he obtained an ordinary Professorship at the University of Breslau; he remained at Breslau until he retired in 1926.

The path that lead Minkowski to discover the role the pancreas has in preventing diabetes began simply enough. In 1889 while working in the medical clinic at Strasbourg, Minkowski needed to consult a journal from the chemistry department library. While there he meet up with his friend Joseph von Mering (1849–1908) who told Minkowski about an oil he had just prepared that he believed would be better than cod-liver oil in treating rickets. In contrast to cod-liver oil, the new preparation did not need a pancreatic enzyme for its absorption into the blood. However, one major difficulty with Mering's idea was that a test would require an animal with its pancreas completely removed. At the time this was an operation generally considered impossible to perform and still have the animal survive.

Minkowski reportedly had remarkable surgical skills, and earlier had successfully removed the livers from geese, where successful implied that the animals survived for some significant period after such an operation. Mering challenged Minkowski's boastful statement that he could also remove an animal pancreas successfully, and immediately offered a dog on which to experiment. The next day Minkowski with help from von Mehring removed the dog's entire pancreas.

After the operation had been completed, von Mering left the area for a short period of time leaving the now pancreas-less dog tied up

in one part of Minkowski's laboratory. The dog soon began to drink enormous amounts of water and to pass large quantities of urine. These "surprising observations" for the dog of polyuria (the copious production of urine), polydipsia (an insatiable demand for water), and polyphagia (extreme hunger) are the characteristic symptoms of diabetes in humans. These three "polys" plus the "surprising sweetness" of the dog's urine that Minkowski attested to by taste, led to the abductive conjecture that *diabetes mellitus* in the dog was produced by the removal of the pancreas; and, as a second part of the conjecture, there must be some type of secretion or other process being performed by the pancreas that prevents diabetes from occurring in healthy animals.

Minkowski carried out several additional experimental procedures, some with von Mering's help and all with a dog as the now preferred animal model. First, there was a quick replication with three additional dogs of diabetes induction through the removal of an animal's entire pancreas. He also showed that merely transfusing blood from a diabetic dog to one that was healthy did not produce glycosuria, a common sign of diabetes indicated by the presence of sugar in the urine. In addition, Minkowski performed several transplantation experiments that involved removing most of the pancreas but attaching subcutaneously a small remaining piece having an intact blood supply to the abdominal wall. No diabetes occurred until the remnant itself was removed suggesting that whatever internal secretion there might be was done directly into the blood supply.

As we now know, the pancreas produces insulin through what are called the islets of Langerhans situated on the surface of the

pancreas. These were named for the German pathological anatomist, Paul Langerhans (1847–1888), who identified their presence in 1869 although he did not know their function as the secreters of insulin. It wasn't until the work of Eugene Opie (1873–1971) in 1900 that it was recognized that diabetes would occur when the islets of Langerhans were destroyed even though the remainder of the pancreas might still be intact.

Based on Minkowski's observations and the hypothesis that the pancreas was the source of secretion(s) that could prevent diabetes, a number of individuals attempted the extraction of such a hypothesized entity from collections of animal pancreases. But it wasn't until some three decades later that such an engineering feat was successfully completed. In 1921 working at the University of Toronto, Frederick Banting (1895–1941) along with a then graduate student, Charles Best (1889–1978), extended Minkowski's experiments and successfully isolated insulin from animal pancreases. More importantly, Banting and Best were able to demonstrate the clinical effectiveness of their extract in the treatment of Type I diabetes.

Banting and Best worked in a lab provided by John Macleod (1876–1935) who at the time was a senior lecturer in physiology within the medical faculty at the University of Toronto. In addition to Banting and Best, Macleod invited a visiting chemist, Bertram Collip (1892–1965), to work on the problem of purification for the extract being produced by Banting and Best from the raw pancreatic material. Banting and Macleod were jointly awarded the 1923 Nobel Prize in Physiology or Medicine for the discovery and isolation of insulin. Banting promptly shared his monetary award with Best;



Macleod did the same with Collip.

The production of enough insulin with sufficient purity even for a clinical verification of effectiveness was a continuing problem for the group at Toronto. It was not until a collaboration with Eli Lilly Pharmaceuticals was formalized that the supply issue was successfully resolved. The head chemist at Eli Lilly, George Walden (1895–1982), developed a process of isoelectric precipitation that eventually allowed the mass production of insulin. Previous attempts at insulin purification in Toronto had tried to keep insulin in solution and precipitate out the contaminating proteins. Walden showed that if the pH level were adjusted to maximize precipitation, the precipitate that resulted contained highly purified insulin that was some 10 to 100 times purer than what was possible before. With the development of isoelectric precipitation the mass production of insulin could be instituted.

The history of insulin discovery is told most definitively by Michael Bliss in his monumental, *The Discovery of Insulin* (The University of Chicago Press; 1982/2007). This history documents all the details of the continuing animosities between Banting, Best, Macleod, and Collip, as well as the many interesting side stories produced over the extended period of insulin's development. One of the most consequential vignettes is a discussion of the first human clinical uses of the Banting/Best extract as partly purified by Collip on Leonard Thompson, a severely diabetic fourteen-year-old who resided in the University of Toronto Hospital. Thompson was brought back from near death, and although he never was a well-controlled diabetic, Thompson eventually lived a normal life for another thirteen years

before a fatal bout of influenza in 1935.

Bliss also presents in some detail the more publicly important success stories of insulin use, particularly after more of it became available through the Eli Lilly process. The most prominent case was probably that of Elizabeth Hughes (1907–1981), the daughter of Charles Evans Hughes (1862–1948), once the U.S. Secretary of State and Supreme Court Chief Justice. Frederick Banting first took on Elizabeth as a private patient beginning in August of 1922, making her the first American as well as one of the initial people in the world to be treated with insulin for Type I diabetes. It is estimated that over her lifetime of 73 years, Elizabeth received some 42,000 insulin shots. Elizabeth Hughes appears most prominently in the 1988 Canadian television movie, *Glory Enough for All*, depicting the discovery and isolation of insulin by Banting and Best. Also, she is the main protagonist in *Breakthrough: Elizabeth Hughes, the Discovery of Insulin, and the Making of a Medical Miracle* (Thea Cooper and Arthur Ainsberg, St. Martin's Press, New York; 2010).

## Chapter 8

# The Construction of the First Antimicrobial Sulfa Drug (1931)

Our ideas are only intellectual instruments which we use to break into phenomena; we must change them when they have served their purpose, as we change a blunt lancet that we have used long enough.

— Claude Bernard (1813–1878)

Gerhard Domagk (1895–1964) received his medical degree from the University of Kiel in 1921. After several minor university positions at Greifswald and Münster, Domagk was appointed director of the Institute of Pathology and Bacteriology in 1927 at IG Farben (also known as Bayer laboratories). Using the same type of industrial search methodology pioneered by Ehrlich, Domagk's mandate was to evaluate dye derivatives, a major product of the company, as potential drugs having therapeutic value. In other words, beginning with some promising class of chemicals (dyes, in this instance) as produced and modified by the two Bayer chemists, Friedrich Mietzsch and Joseph Klarer, Domagk was charged with evaluating the possible medical utility of these substances based on an appropriate animal model for some particular disease.

To screen the many chemical variations produced by Klarer and Mietzsch for antimicrobial activity, mice were chosen as the basic animal model with the ubiquitous *Streptococcus pyogenes* as the primary infecting agent (causing strep throat and puerperal (childbed) fever in humans, among other serious diseases). In the early 1930s, Mietzsch and Klarer synthesized a benzene derivative of an azo dye having the addition of a sulfonamide group as a side chain. It was labelled KL730 (KL for Klarer and later called Prontosil), and patented in Germany by IG Farben in 1932. Although initial experiments in 1931 indicated a rather poor antibacterial effect *in vitro* against bacteria cultures, Domagk tested Prontosil in early 1932 against gram-positive *Streptococcus pyogenes* infected mice and found it to be remarkably effective — of twenty-six infected mice, a single dose of Prontosil to twelve of the infected mice was completely curative whereas the fourteen untreated mice all died.<sup>1</sup>

In the early 1930s, several human clinical uses of Prontosil were conducted by Domagk's colleague Philip Klee in the Wuppertal-Elberfeld Hospital located near the Bayer laboratories. Several of these cures in cases of serious streptococcal infection were truly spec-

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<sup>1</sup>There are two excellent book-length sources that document the development of “sulfa” drugs, a commonly used nickname for sulfanilamide and all of its sulfa containing relatives:

Thomas Hager, *The Demon Under the Microscope: From Battlefield Hospitals to Nazi Labs, One Doctor's Heroic Search for the World's First Miracle Drug* (2006, Three Rivers Press, New York).

John E. Lesch, *The First Miracle Drugs, How the Sulfa Drugs Transformed Medicine* (2007, Oxford University Press, New York).

Defining an *antibiotic* as any substance whether produced naturally or synthesized chemically that can selectively destroy a range of bacterial types within a body without doing major damage to the organism itself, then by this definition sulfa was the world's first antibiotic. The two books just referenced provide the story of sulfa drug discovery starting with the Ehrlich paradigm of “dye as medicine.”

tacular given what was to be expected prior to the availability of Prontosil. These instances of cure include Domagk's own young daughter's generalized streptococcal infection from a needle puncture in her hand, and her avoidance of an arm amputation to save her life. Prontosil became the first commercially available antibiotic when it went on the open market in 1935. Shortly thereafter several similarly impressive examples of its effectiveness were produced. One particularly salient instance was carried out by Leonard Colebrook (1883–1967) working at the Queen Charlotte Hospital in London. In 1935 Colebrook demonstrated the effectiveness of Prontosil against childbed (puerperal) fever by initiating the first systematic clinical trial of any antibiotic and showed a general reduction in death rates due to puerperal fever from 1 in 4 to 1 in 20. In addition to this latter systematic study, a number of one-off cases of remarkable recovery from the use of Prontosil continued to be reported in the newspapers. One prominent example was in the recovery in 1936 from a life-threatening streptococcal infection for Franklin D. Roosevelt Jr., the son of the then President of the United States.

In late 1935 while working at the Pasteur Institute in Paris, Daniel Bovet (1907–1992) was given the task of reproducing the results of Domagk on Prontosil based again on mice as an animal model. In testing a number of compounds derived from Prontosil itself, a group of mice were left over for which none of the derivative compounds were available. Bovet decided fortuitously to just give sulfanilimide by itself, a compound well-known and off-patent since the early 1900s; it was also the same type of sulfa molecule that formed part of Prontosil. As they might say, the rest is history. The sulfa compound by itself did just as well as Prontosil or any of the derivatives being

assessed. It is this latter “surprising” observation of the positive effects of sulfanilimide alone that led to the abductive conjecture that sulfa per se was the “miracle” drug it turned out to be.

The potency of sulfanilamide by itself might (or possibly, should) have been abductively conjectured much earlier from the “surprising” observation that Prontosil worked *in vivo* but not *in vitro* when bacteria were cultured externally in test tubes. Somehow, Prontosil had to be “bioactivated” in the body of an organism and split into parts — one part was the dye itself and the second was the colorless sulfa molecule. It was only the sulfa part that acted against the disease-causing microbes; the dye portion of Prontosil merely colored the organism’s body red and had no discernible effect on a disease.

The availability of sulfa drugs produced outside of Germany proved crucial to the allies in the Second World War. Sulfa was part of every soldier’s emergency medical kit, and was used both internally and on external wounds resulting from combat. The specific sulfa drug available was sulfapyridine, a first generation sulfonamide antibiotic. It was commonly called M & B 693 in reference to the British pharmaceutical company, May & Baker, which produced large amounts of the drug as part of the overall war effort.

In late 1943 at the height of the second World War, a sixty-nine year-old Winston Churchill traveled to several locales in the Middle East to meet and consult with several of Britain’s allies – Chiang Kai-shek, Stalin, and Franklin Roosevelt. Given the strenuous travels this required, Churchill came down with a serious case of pneumonia but survived after receiving doses of M & B 693 from his doctors Evan Bedford and McMoran Wilson, who attended to Churchill’s illness.

When Churchill flew to Marrakesh to continue his convalescence, he issued the following bulletin which appeared in various British newspapers:<sup>2</sup>

This admirable M&B, from which I did not suffer any inconvenience, was used at the earliest moment; and after a week's fever the intruders were repulsed. I hope all our battles will be equally well conducted. The M&B, which I may also call Moran and Bedford [Churchill could not resist the joke on his physicians' names], did the work most effectively. There is no doubt that pneumonia is a very different illness from what it was before this marvelous drug was discovered.

Besides the various sulfa-derived drugs being produced from the late 1930s to the early 1940s, it was also discovered how such a sulfa drug actually worked which in turn led to a whole new approach to drug design. A pair of London researchers, Donald Woods and Paul Fildes, noted the “surprising” observation that sulfa never did well in the presence of a lot of pus and dead tissue, typical of an uncleaned combat wound. The abductive conjecture was made that some type of anti-sulfa substance must therefore be present. This substance was explicitly identified as a sulfa-twin called para-aminobenzoic acid (PABA) which was intimately involved in bacterial metabolism. Sulfa worked because it looked like PABA, and therefore was taken up by bacteria that could not produce their own, and were eventually starved to death. In dead pus-filled wounds there was lots of PABA around so the sulfa was not taken up as readily and therefore could not starve out the bacteria.

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<sup>2</sup>This quote and the included aside are given on page 159 in the John Lesch book cited in the previous footnote

The initial surprising observation of PABA presence led to a search for similar impostor molecules that would substitute for the needed bacterial foodstuffs. This whole process could be considered an “anti-metabolite” approach to drug discovery: whenever bacteria could make their own PABA, they would not be affected by sulfa or any similar impostor molecules. This strategy of rational drug discovery avoids what might be considered the “fallacy of dye as drug” that goes all the way back to Ehrlich; the azo dyes were also the initial basis for Prontosil. The group at Bayer including Domagk were committed to the conjecture that therapeutic activity was linked to the coloring produced by the azo dye derivatives being tested. This approach might be called the “myth and fascination of color” which began with Ehrlich and his obsession with tissue staining that used dyes such as methylene blue and typan red.

Gerhard Domagk was awarded the 1939 Nobel Prize in Physiology or Medicine for his “recognition of the anti-bacterial activity of Prontosil.” Unfortunately, Domagk was forced to decline the award based on a direct order from the Hitler regime. At the end of the second World War in 1947, Domagk was finally able to travel to Sweden to receive belatedly the Nobel Prize and to give the customary address. In his lecture, Domagk discussed his current work on combating tuberculosis with a particular chemical, thiosemicarbazone, commonly called Conteben. He also presciently discussed the development of antibiotic drug resistance in a bacterial strain, particularly for patients who do not attend to and complete a full course of treatment.

There is one more seminal incident involving sulfa as a drug that deserves mention. Because sulfanilamide and its variations were all



off-patent, they could be produced and sold without any further restrictions. One such sulfa variation in liquid form, Elixir Sulfanilamide, was produced in 1937 by S.E. Massengill Company in Bristol, Tennessee. The liquidity of the sulfa compound was produced through the use of diethylene glycol, a deadly poisonous chemical commonly used as an antifreeze. At the time no safety studies were required before a new drug could be introduced to the market. Because of the lack of regulation on the sale of new drugs, well over one-hundred people died after consuming Elixir Sulfanilamide and before the remaining stock of the liquid could be recalled. Due primarily to this unfortunate incident, the U.S. Congress passed the 1938 Federal Food, Drug and Cosmetic Act that is still in force to the present. This Act requires a proof of safety certificate from the U.S. Food and Drug Administration (the FDA) prior to any new drug being released for commercial sale.

## Chapter 9

# The Development of Warfarin As a Blood Anticoagulant (1933)

If I didn't believe it, I wouldn't have seen it.

— Yogi Berra

In the early 1920s, the northern plains of the United States and the extension into Canada saw an outbreak of a previously unknown hemorrhagic cattle disease. Cattle were fatally bleeding out after minor surgical procedures, and some were just dying spontaneously. An astute Canadian veterinary pathologist, Frank Schofield (1889–1970), conjectured at the time that the disease was not due to any pathogenic organism or to a nutritional deficiency but rather the malady was the result of cattle ingesting moldy silage made from sweet clover. Somehow the spoiled clover was acting as a powerful anticoagulant. Schofield proceeded experimentally to show the effect of moldy silage by feeding rabbits both spoiled and unspoiled sweet clover and noting the differential fatal hemorrhaging that resulted. The specific anticoagulant substance present in the tainted silage, however, was never identified.

In the early months of 1933 the story of warfarin's eventual discovery moves to the biochemical lab of Karl Paul Link (1901–1978) at the University of Wisconsin in Madison. Link had a professorial appointment at Wisconsin since 1927, and although working mainly on plant carbohydrates, he knew of the “sweet clover disease” studied by Schofield. Link was working at the time with several members of the Genetics Department at Wisconsin on a different sweet clover problem – its bitterness of taste that made it less than ideal as a livestock feed. It was against this background that on a Saturday afternoon in February of 1933, a farmer named Ed Carlson appeared on Wisconsin's campus hoping to get help from the Agricultural Experiment Station on the hemorrhagic disease then ravaging his farm. Given that it was Saturday, the office of the State Veterinarian was closed; but, by chance, farmer Carlson ended up at the Biochemistry Building and to the then open and active lab of Karl Link.

Farmer Carlson had brought with him multiple pieces of evidence for a sweet clover disease: a dead heifer, a milk can full of blood with no apparent clotting capacity, and about one-hundred pounds of spoiled sweet clover, the only hay he had available to feed his cattle. At the time, the sole piece of advice Link was able to give Carlson was to stop using the spoiled hay and to transfuse those seriously sick cattle that he wished to save. Although not a satisfactory solution for farmer Carlson, this episode set Link and his several talented graduate students on a path that would eventually lead to the development of the blood anticoagulant warfarin.

The abductive “working” hypothesis followed by Link should be obvious: some specific anticoagulant substance must be present in

moldy sweet clover based on the “surprising” observations of animals invariably coming down with a hemorrhagic disease after ingesting spoiled silage. The issues of actually identifying the anticoagulant and eventually being able to synthesize it were quite different matters, however. The path was long and arduous between that Saturday in February of 1933 when Carlson had visited the Link lab, and six years later when a graduate student, Harold Campbell, was finally able to see a small amount of crystalline dicumarol on a microscope slide. The anticoagulant dicumerol is produced by a fungal mold acting on the natural coumarin present in sweet clover; it is the coumarin that gives the familiar sweet smell of newly mown hay.

Another graduate student in the Link lab, Mark Stahmann, was put in charge of the mass isolation of dicumarol. Several grams of the crystalline anticoagulant were naturally produced before it was then eventually synthesized in April of 1940 by another of Link’s graduate students, Charles Huebner. It was the explicit knowledge of the chemical composition of dicumarol that allowed some one hundred and fifty variants to be produced having a range of anticoagulant properties, including number 42 that was eventually named warfarin.

Once synthesized and beginning in 1940, dicoumarol was subjected to extensive clinical trials at both the Mayo Clinic and the Wisconsin General Hospital. Using rabbits, Link had shown that the anticoagulant effects of dicumarol were quickly reversible by the administration of vitamin K; thus, human clinical trials could proceed with some available safety controls. Dicumarol soon became for its time the most popular prescribed oral anticoagulant. Because of its high toxicity the chemically similar variant, warfarin, was patented in 1948

only as a rat poison by the university entity that had funded Link's lab over the years — the Wisconsin Alumni Research Foundation.<sup>1</sup>

As just noted and because of warfarin's assumed high toxicity, it was initially marketed solely as a rodenticide under the brand name of d-Con. Then, in 1951, an army recruit tied to commit suicide by ingesting large amounts of warfarin (in the form of d-Con) but survived. This poor individual had unwittingly become the “poster child” for the human use of warfarin as an oral anticoagulant. The fate of warfarin was eventually sealed as the most important oral anticoagulant in the late 1950's and beyond when it was administered to then President Dwight Eisenhower in 1955 after he had a heart attack while visiting relatives in Denver. Warfarin is still one of the most widely prescribed oral anticoagulants and is marketed under the brand name of coumadin, among others.

One of the more speculative uses of warfarin suggested recently is in the mechanism by which Stalin might have been assassinated in 1953, presumably by one of his close intimates that included Nikita Khrushchev and Georgi Malenkov among a few others. In the book, *Stalin's Last Crime: The Plot Against Jewish Doctors, 1948–1953*, Jonathan Brent and Vladimir Naumov conjecture on the need

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<sup>1</sup>The discovery of vitamin K is itself a nice exemplar of abductive reasoning. The Danish physiologist Henrik Dam (1895–1976) was engaged in nutritional experimentation that required feeding a cholesterol-free diet to chickens. He noted the “surprising” observation that chicks fed the fat-depleted chick chow developed hemorrhages and started serious bleeding. Dam abductively conjectured that in addition to the removal of the cholesterol from the feed, a second compound, a vitamin, had also been removed that controlled coagulation. He named this removed component vitamin K for the German word “Koagulation.” (Because Dam first published his discovery in a German journal, the letter “K” was an apt descriptor.) Dam eventually received the 1943 Nobel Prize in Physiology or Medicine for his vitamin K discovery.

to kill Stalin to prevent a nuclear war with the United States. Stalin had spun a vast conspiracy theory involving Soviet Jews who were supposedly under the secret direction of the United States, and which involved a plot to kill him and completely destroy the Soviet Union. Brent and Naumov speculate on the lacing of Stalin's drinks with tasteless warfarin over a number of late-night dinners with his immediate colleagues. At the time, warfarin was being heavily marketed and available worldwide as an effective rodenticide.

There are several published sources that detail the discovery by Link and his graduate student colleagues of dicumarol and its variants, such as warfarin. One such narrative is by Link himself: *The Discovery of Dicumarol and Its Sequels* (*Circulation*, 1959, 19, 97–107); the second is a National Academy of Sciences Biographical Memoir written in 1994 by a fellow Wisconsin faculty member, Robert H. Burris: *Karl Paul Link, 1901–1978*.

## Chapter 10

# The Path of Discovery for the Antibiotic Streptomycin (1943)

The Lord hath created medicines out of the earth; and he that is wise will not abhor them.

— Ecclesiasticus 38:4

Throughout recorded history the soil that surrounds us all has been the source of many “surprising” observations about its phenomenal ability to decompose myriad forms of organic matter. The composting and putrefaction of organic material generally leads to the end product called humus, and eventually to the nourishment of new cycles of reanimated life. As has been known from at least the invention of the microscope, soil contains an innumerable number and variety of microbes. Some of these may be antagonistic to one another and some may be benign or even beneficial. The abductive conjecture that results from these common but “surprising” observations about organic matter decomposition is that such a process of decay must be guided by chemical substances produced by the microorganisms present in the soil. Or, to state a simple working hypothesis in a slightly different way, because soil is a self-purifying environment, it should be able to supply agents, or in Paul Ehrlich’s terms, “magic

bullets,” that can destroy all manner of microorganisms including those that cause disease.

Stemming from the basic conjecture that chemicals produced by soil microbes somehow guide the process of putrefaction, the question then arises as to the possible isolation of these various agents and the identification of what effects they might have on a range of disease-causing entities. The search typically involves the use of common laboratory Petri dishes having two layers imbedded in an agar culture medium – one layer contains a soil sample and the second is typically seeded with some form of disease-causing bacterial substance. If it is clear that something in the soil has compromised the bacterial layer by producing, say, a “hole,” then further attempts can be made to isolate and culture that specific soil microbe, which may again be tested against the disease-causing bacterial substance.

Once a pure culture of a candidate soil microbe is available, further attempts can then be made to extract the antagonistic chemical itself from these cultures. When such an extraction is available in sufficient quantities, it could then be used, for example, in further animal trials to test both for toxicity and effectiveness. When possible, a successfully extracted chemical would lead to a synthesized compound having the same composition as that identified through the naturally occurring culturing process. In the final stages of human clinical trials, it is hoped that an isolated substance would be curative for some particular class of disease-causing entities but yet not too toxic on the human body itself.

The two individuals most identified historically with exhaustive searches for medically significant microbes through the processing of



soil samples are Selman Waksman (1888–1973) and his early doctoral student René Dubos (1901–1982). Waksman was born to Jewish parents in the Ukrainian Kiev Governorate of the Russian Empire. After receiving his gymnasium diploma in Odessa in 1910, Waksman immigrated to the United States and became a naturalized citizen six years later. He received a Bachelor of Science degree in agriculture in 1915 from Rutgers College (now University) and proceeded to a Master's Program in soil bacteriology at the New Jersey Agricultural Experiment Station. After receiving a doctoral degree in biochemistry from the University of California at Berkeley in 1918, Waksman rejoined the faculty at Rutgers University in the Department of Biochemistry and Microbiology.

After completing his doctoral degree under Waksman in 1927, the French-born René Dubos was recruited to the Rockefeller Institute in New York City by Avery Oswald. Oswald challenged Dubos to find a soil microbe able to destroy the durable polysaccharid capsule of the type III pneumococcal bacteria. Although Dubos was eventually successful, the enzyme isolated was difficult to purify and detoxify and was soon overshadowed by the newer development of the antibacterial sulfa drugs. Dubos was more generally successful in 1939 in isolating two substances, tyrocidin and gramicidin, from the soil microbe *Bacillus brevis* which were both active against gram-positive organisms. Although these two antibiotics are generally too toxic for internal use in humans, gramicidin still finds extensive application in externally applied antimicrobial ointments. These two antibiotic substances systematically cultivated from soil bacteria were the first to be so obtained from natural sources through rational pursuit and

then produced commercially. Howard Florey credits Dubos' success with gramicidin for reviving his own stalled research on penicillin; similarly, Waksman himself would be spurred in his search for a soil microbe that would be effective against the bacillus causing tuberculosis.

The soil microbes of most interest to Waksman were actinomycetes which are life forms somewhere between fungi and bacteria. Waksman's research was directed to the identification of a microorganism from this class that would hopefully have an antibiotic effect against gram-negative bacteria generally, and possibly against the specific bacillus responsible for tuberculosis. A graduate student named Albert Schatz (1920–2005) working in Waksman's lab under the usual soil search protocol took on this latter task. Rather remarkably, Schatz identified the antibiotic streptomycin in October of 1943, after just several months of laboratory effort.<sup>1</sup> Among all the dozen or so antibiotics developed between 1940 and 1952 from actinomycetes in Waksman's laboratory, streptomycin was by far the most important. It was the first antibiotic discovered that was at all effective against gram-negative bacteria and the causes of such historically important diseases such as the bubonic plague, cholera, and typhoid fever; most importantly, it was also active against the tuberculosis bacillus.<sup>2</sup>

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<sup>1</sup>It is of some interest to note that Schatz did not obtain his particular actinomycete organism from a soil sample. It came from a fellow researcher named Doris Jones who found it in the throat of a sick chicken.

<sup>2</sup>There are several books that discuss the general development of antimicrobial medicines as well as the more specific search for an effective cure for tuberculosis. Two of the best that comprehensively discuss drug development during the twentieth century are:

Frank Ryan (1993), *The Forgotten Plague: How the Battle Against Tuberculosis Was Won – and Lost* (Little, Brown and Company, Boston)

Streptomycin was first reported in the medical literature by the Rutgers group in January of 1944. Within months extensive animal trials using guinea pigs were being carried out at the Mayo clinic by H. Corwin Hinshaw and William Feldman. In addition, several isolated human uses of streptomycin were also conducted at the end of the Second World War by the United States Army to treat life-threatening infections at a military hospital in Battle Creek, Michigan. Interestingly, the third person so treated was Robert Dole, the later majority leader of the United States Senate and presidential nominee. The first randomized trial of streptomycin against pulmonary tuberculosis was carried out in the late 1940s by the Medical Research Council (MRC) Tuberculosis Research Unit in the UK. In this first ever randomized clinical trial, subjects were chosen at random as to who would receive streptomycin and who would not. At the time this was deemed ethical because of the very limited amount of the antibiotic that was then available, and therefore, not everyone could be treated.<sup>3</sup>

René Dubos would go on in the later part of his long career to become one of the world's first and best-known environmentalists. He is remembered for coining the phrase: “think globally, act locally.”

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William Rosen (2017), *Miracle Cure: The Creation of Antibiotics and the Birth of Modern Medicine* (Penguin Books, New York)

<sup>3</sup>This first randomized clinical trial was overseen by the English epidemiologist and statistician, Sir Austin Bradford Hill (1897–1991). Hill served as a pilot in the first World War but was invalided out when he contracted tuberculosis. After two years in the hospital and two years of convalescence, Hill took a degree in economics by correspondence from London University. Hill is well-known for the MRC Tuberculosis Study and for his work with Richard Doll on the connections between lung cancer and cigarette smoking. He also wrote the highly influential textbook, *Principles of Medical Statistics*, and for developing the “Bradford Hill” criteria for determining the validity of causal associations.

In 1950 Dubos published one of the best of Pasteur's many biographies: *Louis Pasteur, Free Lance of Science*; he also won the 1969 Pulitzer Prize for General Non-Fiction for his book, *So Human an Animal*.

In contrast to the remarkable career of Dubos, Albert Schatz after his receipt of a doctoral degree from Rutgers in 1945 based on his discovery of streptomycin, went on to develop a mediocre scientific record. Schatz, however, believed that he was left out of all the rewards that his discovery of streptomycin had led to, irrespective of all the other many antibiotics discovered in Waksman lab using exactly the same soil search methodology that Schatz had been taught. Nevertheless, Schatz sued both Waksman and the Rutgers Research and Endowment Foundation demanding credit as co-discoverer of streptomycin and a share in the royalties received for the antibiotic. By the end of the lawsuit, Waksman would receive a 10% royalty, Schatz got 3% and the remainder of the lab shared in 7% with the rest reverting to the Rutgers Foundation. However these royalties were shared and irrespective of Schatz's bitter denunciations, Waksman become the sole recipient of the 1952 Nobel Prize in Physiology or Medicine for the discovery of streptomycin.

As of today, tuberculosis remains the number one world-wide cause of infectious disease death, and is still deserving of the name "The Great White Plague." Unfortunately that status is hard to change given the problem of antibiotic drug resistance that has developed particularly in the presence of other diseases such as HIV. Streptomycin is still generally effective but must be used in conjunction with other drugs, such as isoniazid and PAS (para-amino salicylic acid).

In poor and developing countries this type of combination therapy may be hard to come by.<sup>4</sup>

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<sup>4</sup>A bill passed in the New Jersey State Legislature in 2017 has named *Streptomyces griseus* obtained from soil actinomycetes as the New Jersey State Microbe in honor of it being discovered in New Jersey soil and streptomycin being isolated from it in a New Jersey laboratory facility.

# Chapter 11

## The Origins of Chemotherapy (1944)

But in science the credit goes to the man who convinces the world, not to the man to whom the idea first occurs.

— Sir Francis Darwin (1848–1925)

In December of 1943 during the second World War, the Adriatic harbor of Bari on the eastern coast of southern Italy was filled with Allied ships waiting to unload their cargoes in support of a military push up the “Italian boot.” Among the vessels moored in the harbor was the American Liberty Ship, John Harvey, clandestinely carrying 540 tons of mustard gas bombs. The Allied Command reasoned that in the event the retreating German Army might resort in desperation to the use of chemical weapons in contradiction of the 1925 Geneva Protocol, the mustard gas stockpiled aboard the John Harvey could then be deployed immediately in direct retaliation. On the evening of December 2, 1943, a massive wave of Luftwaffe bombers attacked Bari Harbor, blowing up and sinking some seventeen ships including the John Harvey and its stored mustard gas. This lethal cargo along with the oil from the many other destroyed ships provided a deadly solution that drenched hundreds of men who had survived the initial explosions.

The survivors from the ships in Bari Harbor, covered as they were for a substantial period of time with oil and mustard gas solutions, soon developed a variety of serious medical conditions. To help with the medical treatment for these individuals, the Allied Force Headquarters at Algiers sent Lieutenant Colonel Stewart Alexander (1914–1991), a young doctor then affiliated with the U.S. Army Chemical Warfare Service. Using rabbits as an animal model, Alexander had been studying for several years the effects of the compounds present in chemical weapons, such as in mustard gas. Alexander therefore had some knowledge of the effects of such chemicals and possible treatments. It was also thought that he might be able to tell whether the Germans had purposely used chemical warfare in their attack on Bari Harbor.

Alexander (abductively) conjectured that the Bari deaths subsequent to the initial explosions were generally caused by a reaction to the chemical agents in mustard gas absorbed through the skin. Furthermore, by mapping the locations of the ships that were sunk and the areas from where the victims were rescued, Alexander was able to identify the mustard gas as coming from the John Harvey, now strewn over the bottom of Bari harbor, and not from any German aircraft involved in the attack.

Although the presence of mustard gas at Bari was never publicly acknowledged by the Americans or the British, Alexander nevertheless wrote a formal but classified report on the victims at Bari. He noted in particular that the symptoms seen at Bari were much more severe than those usually occurring with mustard gas. Also, Alexander made a “surprising observation” that was to eventually lead to

the development of chemotherapy for various forms of cancer. He noted an inexplicable drop in human white blood cell counts, similar to what he had witnessed in his earlier experiments with rabbits — white blood cells seemed to just disappear and lymph nodes “just melted away.” These effects of mustard gas had not been seen before in the first World War when deaths due to chemicals were caused by the inhalation of caustic vapors. In Bari, victims had absorbed the chemicals present in mustard gas directly through their skin as a result of the long period of exposure through contaminated harbor water soaked into the clothes they wore continuously.

The “surprising observation” of a dramatic reduction in white blood cells first led Alexander to the (abductive) conjecture that such an agent present in mustard gas might be the cause of such a decrease. Then, assuming this conjecture to be true, these agents could prove useful therapeutically in treating those (cancer-like) diseases characterized by the overproduction of certain cells. These observations, although still classified, were picked up and recognized for their importance by Alexander’s boss, Dr. Cornelius Rhoads (1898–1959), then overall head of the Chemical Warfare Service, and, at the time, one of the world’s leading cancer researchers. Rhoads would soon become the director of the Sloan-Kettering Institute for Cancer Research located in New York City. In this capacity after the conclusion of the second World War, Rhoads would oversee the research leading to the present-day applications of chemotherapy as applied to various forms of human cancer.

After his military service in the second World War ended, Alexander never continued a research program involving chemotherapy, but



it was clearly his “prepared mind” and “surprising observation(s)” about the precipitous reduction in white blood cells that were a major impetus to the development of chemotherapy as it is practiced today. For a comprehensive narrative on Alexander and Rhoads and the path to present-day cancer treatment, see Jennet Conant, *The Great Secret: The Classified World War II Disaster that Launched the War on Cancer* (2020; W. W. Norton & Company, New York).

## Chapter 12

# The Discovery of Cephalosporin Antibiotics (1948)

The eye sees only what the mind is prepared to comprehend.

— Henri Bergson (1859–1941)

During the first half of the Twentieth Century, Giuseppe Brotzu (1895–1976) served as a Professor of Hygiene at the University of Cagliari on the Italian island of Sardinia; also, he was the Rector for the whole University during the period encompassed by the Second World War. At the end of the war, Brotzu became the superintendent of public health for the city of Cagliari, with responsibility for overseeing the disposal of local sewage. At the time, all such raw effluent was merely emptied into the ocean untreated.

It was in this capacity as head of public health for the city of Cagliari that Brotzu made his “surprising observation” which would eventually lead to his discovery of the cephalosporin class of antibiotics. Brotzu noted that the sewage being emptied untreated into the ocean seemed to have some capacity for self-purification. All of the many young swimmers at Su Succi Beach near the raw effluent outlet never appeared to get sick. In particular, the disease of typhoid fever

which was more or less endemic to the area never seemed to affect any of the swimmers near the sewage outfall.

Brotzu's (abductive) conjecture for explaining the swimmers' apparent protection against disease was that some type of fungus or other living material present in the sewage somehow negated the disease entities that might have been present. Based on this hypothesis of self-purification, Brotzu collected various samples from the effluent entering the ocean near the Su Succi beach. After a short period of time culturing the effluent in 1945, he was able to isolate a candidate fungus, *Cephalosporium acremonium*, that produced a substance antagonistic to many bacteria, including the bacillus causing typhoid.

Somewhat akin to Fleming who named the antibiotic penicillin before he had isolated it in a pure form from a *Penicillium* mold, Brotzu named his antibiotic substance cephalosporin before producing it in a refined form. He was, however, able to show that a crude fungal broth had no toxicity and was effective in treating boils and local infections. Unfortunately, when administered internally the crude fungal broth produced a variety of allergic reactions in addition to whatever possible mitigating effects the impure mixture might have had on a patient's disease, such as typhoid.

Brotzu could not convince the Italian pharmaceutical industry to take an active interest in his discovery and assist in isolating a pure form of the active ingredient which could then be studied further. As an alternative, Brotzu enlisted the assistance of Dr. Blyth Brooke who had been a British Public Health Officer in Sardinia during the Second World War. Brooke wrote to the Medical Research Council in London on Brotzu's behalf. In turn, the Council suggested that

the research group headed by Howard Florey at Oxford be contacted. This group had been responsible for the earlier viable development of penicillin. So, in September of 1948, a fungal culture plus a report written by Brotzu on the effectiveness seen thus far for the fungal material he had isolated from the raw sewage flowing into the ocean at the beach at Su Succi. The conclusion of the report read as follows:

The results of the present studies appear to suggest that this antibiotic principle produced from *Cephalosporium acremonium* may have a very extensive range of application.

Its in-vitro activity against staphylococci, streptococci, ... , and its efficacy in staphylococcal and streptococcal infections, typhoid fever and brucellosis, as well as in-vivo trials in human subjects, despite the limitations due to difficulties in extracting the antibiotic principle, suggest that this antibiotic may have a distinctly promising therapeutic potential.

*These findings have been reported here in the hope that other better equipped institutes may be able to make greater progress in the selection of the fungus and in the culture preparation and extraction of the antibiotic.* (italics in the original)

The Oxford group eventually isolated several forms of cephalosporin — for example, P (for gram-positive bacteria). N ( for gram-negative bacteria), and C. Many additional generations of cephalosporin antibiotics have been developed over the years by large pharmaceutical companies such as Eli Lilly in the United States.<sup>1</sup>

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<sup>1</sup>The report quoted above that Brotzu sent to Florey was an invented journal for that explicit purpose, and in its total existence published only the one 1948 paper by Brotzu passed along to Florey. For several sources relating the history behind the development of cephalosporin antibiotics, see Robert Winters, *Accidental Medical Discoveries*, 2016, pp. 107–112; and M. Lawrence Podolsky, *Cures Out of Chaos*, 1997, pp. 213–216.

## Chapter 13

# The Road to Lithium – the First Effective Medication for a Mental Illness (1949)

Lithium is the penicillin story of mental health.

— Greg de Moore and Ann Westmore

I am not a scientist. I am only an old prospector who happened to pick up a nugget.

— John Cade

John Cade (1912–1980) was an Australian psychiatrist who in the late 1940s discovered the use of lithium as a mood stabilizer in the treatment of bipolar disorders. Lithium through one of its salts such as lithium carbonate, has the distinction of being the first effective medication to treat a mental illness. A century before Cade's discovery of lithium as a mood stabilizer, it had been considered as a possible medical treatment for gout, a condition caused by the deposit of uric acid crystals in various joints of the human body. At least in the laboratory, lithium had shown an ability to dissolve uric acid crystals isolated from the kidneys. Unfortunately, because the amount of lithium needed to dissolve uric acid within the human

body would be toxic, such possible uses for lithium were abandoned by the turn of the century. These two notions of lithium toxicity and its ability to dissolve uric acid will be revisited as part of John Cade's discovery of lithium as a treatment for bipolar disorders.

John Cade received his medical degree with an emphasis in psychiatry from the University of Melbourne in the middle 1930s. He practiced medicine as a house officer for several small institutions before joining the Australian Army Medical Corps in 1940 as part of Australia's general mobilization efforts for the Second World War. When imprisoned by the Japanese at Changi Prison in Singapore from 1942 to 1945, Cade saw many of his fellow inmates exhibiting various forms of strange ("surprising") behavior that he abductively attributed to malnutrition and chemical or toxin imbalances that affected their brains. It was this general belief in a chemical cause for mental illness that would eventually lead to Cade's identification of lithium as a mood stabilizer.

After the war, Cade took up a position at the Bundoora Repatriation Mental Hospital in Melbourne. Based on his overall view that mental disturbances were most likely chemically induced much as in having an over- or under-active thyroid, Cade proceeded to regularly collect concentrated morning urine from all the patients at Bundoora, and to then store the urine in the Cade family's refrigerator on the Bundoora campus. Using a primitive shed near his residence as an animal shelter, Cade injected the urine-based solutions into the abdomens of guinea pigs in an attempt to discover the differing strengths of the waste products such as urea and uric acid for the types of mental patients providing the urine. Presumably the

more toxic waste products would be coming from the more manic or distressed mental patients. Any concentrated urine in a sufficient quantity would kill a guinea-pig but urine from a manic patient conjectured to be producing too much of some toxic substance would presumably kill even more readily.

After a number of variations of this urine injection protocol which considered uric acid as a putative modifier of urea toxicity that was made soluble through the use of lithium urate, Cade fortuitously injected the guinea pigs in a supposed control condition with only the lithium carbonate. This latter solution by itself appeared to make the guinea pigs extremely docile and restful and provided a set of “surprising observations” that Cade interpreted as a calming effect for lithium carbonate as opposed to being just due to the toxicity of the injected chemical. These were the key observations that led Cade to consider (or abductively conjecture) lithium as a possible calming medicine for his most distressed patients evincing the mania of a bipolar disorder.

Based on the initial observations of a calming effect on guinea pigs after lithium carbonate injection, Cade first proceeded to self-test the human toxicity of lithium by ingesting various doses himself. Convinced of safety from these self-trials, Cade began to treat with remarkable initial success a long-term bipolar disorder patient in residence at Bundoora, William (Bill) Broad. Subsequent to this first case, Cade initiated a small trial involving lithium citrate and/or carbonate on Bundoora patients with diagnoses of mania, melancholia, or schizophrenia. The calming effect was so robust in this first trial that Cade even speculated that mania may be due to a deficiency in

lithium per se.

In 1949 Cade published a short paper on this first small lithium trial in the *Medical Journal of Australia*, entitled “Lithium salts in the treatment of psychotic excitement.” The short ending discussion section from this paper is reproduced below:

There is no doubt that in mania patients’ improvement has closely paralleled treatment and that this criterion has been fulfilled in the chronic and subacute cases just as closely as in the cases of more recent onset. This quietening effect on restless non-manic psychotics is additional strong evidence of the efficacy of lithium salts, especially as such restlessness returned on cessation of treatment.

Lithium salts have no apparent hypnotic effect; the result is purely sedative. The effect on patients with pure psychotic excitement — that is, true manic attacks — is so specific that it inevitably leads to speculation as to the possible etiological significance of a deficiency in the body of lithium ions in the genesis of this disorder.

Lithium may well be an essential trace element. It is widely distributed, has been detected in sea-water and in many spring and river waters, in the ash of many plants and in animal ash.

Pre-frontal leucotomy [lobotomy] has been performed lately on restless and psychopathic mental defectives ... in an attempt to control their restless impulses and ungovernable tempers. It is likely that lithium medication would be effective in such cases and would be much preferred to leucotomy.

It would take some twenty years after this first Cade publication before lithium was widely adopted in psychiatry. One major difficulty was lithium toxicity that led to the deaths of several patients undergoing lithium treatment. The problem of lithium toxicity was greatly reduced once suitable procedures were in place to monitor and measure lithium blood levels. A second issue was the natural



occurrence of lithium as a basic element which prevented lithium salts from ever being patented. Because of this, lithium had no large commercial pharmaceutical appeal, and the drug industry had little monetary incentive to promote lithium therapy.

Another obstacle in the adoption of lithium as a treatment in psychiatry occurred in the late 1940s when a “toxicity panic” appeared in the United States when lithium chloride was considered as a dietary substitute for the more medically destructive sodium chloride (common table salt). Because of a lack of any dosage control, toxic reactions soon appeared. The United States Food and Drug Administration (the FDA) ordered lithium salts off the market in 1949. It would take until 1970 for the FDA to again allow such lithium products back but now only in controlled medicines where presumably lithium blood levels would be monitored in a patient.

After the appearance of Cade’s first paper in 1949, there were several additional observational studies published in Australia and England of lithium’s effectiveness in treating bipolar disorders. It was not until 1954 in Denmark, however, that Mogens Shou and colleagues carried out the first randomized clinical trial (RCT) of lithium at the Aarhus University Psychiatric Hospital. This first RCT trial in psychiatry was double-blinded where neither doctors or patients knew whether lithium or a placebo was being administered. This study showed a definitive antimanic therapeutic value for the use of lithium. The introductory paragraphs of this first RCT for lithium are given below:<sup>1</sup>

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<sup>1</sup>The Treatment of Manic Psychoses by the Administration of Lithium Salts, M. Schou, et al., *Journal of Neurology, Neurosurgery, & Psychiatry*, 1954, 17, 250–260.

The treatment of manic psychoses with lithium salts was introduced by Cade in 1949, following an accidental observation of a sedative-like action of lithium ions when administered to guinea-pigs. Beneficial effects of this treatment in cases of mania have also been reported by Ashburner (1950) and by Noack and Trautner (1951).

According to these reports the effects of lithium treatment are striking, and it is rather astonishing that this observation has failed to arouse greater general interest among psychiatrists. One possible reason may be that the doses reported necessary for a clinical effect are close to those giving rise to toxic symptoms. Another explanation may possibly be found in the difficulties encountered in attempts to convey to others in a quantitative manner the clinical impressions of the effect of a new psychiatric therapy. The proper evaluation of a psychiatric therapy is a matter of considerable difficulty for the following reasons: (1) An objective, quantitative assessment of the degree of the psychosis is often difficult or impossible, and usually the evaluation of the effect of a new therapy has to be based on a clinical estimate. (2) Unless special precautions are taken, the therapeutic effect and its evaluation are liable to gross distortions due to suggestibility, negative or positive, in the patients as well as in the observers. (3) Most psychoses, and notably manias and depressions, show spontaneous variations in duration and intensity. For this reason it is not always evident whether an improvement occurring concomitantly with the administration of a certain therapy is spontaneous or due to the therapy given. The purpose of the present study has been to try out the lithium treatment of manic psychoses in such a way that these sources of error and uncertainty were reduced as much as possible.

There is one final aspect of the lithium story as it relates to the abductive reasoning steps of first seeing a set of “surprising observations,” developing a hypothesis to explain these observations, and then relying on the conjecture itself to further substantiate the use-

fulness of lithium treatments as prophylactic agents against recurrent episodes of depression and not just against the occurrence of manic highs. The two Danish psychiatrists, Mogens Schou and Poul Christian Baastrup, both noted that a reduction in manic episodes also appeared to be associated with some attenuation of recurrent depressive periods. A short section given below is from *The History of Lithium Therapy* ( F. Neil Johnson, pp. 71–72) that gives Baastrup’s personal communication to Johnson about his first “surprising observations” as to lithium having some prophylactic effects against depressive episodes. These were followed up by Baastrup and Schou in several formal publications in the 1960s:

... I conducted a follow-up examination on patients who had been discharged from hospital. After a short course of treatment at the out-patient clinic, they had been asked to stop taking lithium. There were two reasons for this examination: firstly, to make sure that patients did not continue to take lithium without the check-ups, and secondly, to see if lithium treatment had caused any undesirable late side effects or other complications. The result was hair-raising. Eight patients, all with a bipolar course, had continued to take lithium and two of them had even bestowed these ‘miracle pills’ upon manic-depressive relatives. None of these people had had any kind of check-up, of course. Their reason for continuing the treatment in spite of our agreement was consistent: all of them said that continuous lithium treatment *prevented psychotic relapse* (italics in the original).

...

I decided to carry out a retrospective study over a period of three years on high-risk patients who at that time were on lithium. The claim that lithium had a prophylactic effect on psychosis had to be tested. In case the result of the retrospective study was positive, against my expectations, I decided to select a group of high-risk

manic-depressive patients for a parallel prospective trial.

There are three rather comprehensive book sources on the evolution of lithium therapy that might be consulted for further detail:

F. Neil Johnson (1984). *The History of Lithium Therapy*. The Macmillan Press, London.

Greg de Moore and Ann Westmore (2016). *Finding Sanity: John Cade, lithium and the taming of bipolar disorder*. Allen & Unwin, Sydney.

Walter A. Brown (2019). *Lithium: a doctor, a drug, and a breakthrough*. Liveright Publishing Corporation, New York.

## Chapter 14

# How Synthetic Psychotropic Drugs Affecting a Person's Mental State First Came to Be (1950)

No more running for the shelter of a mother's little helper.  
They just helped you on your way, through your busy dying day.  
— Mick Jagger/Keith Richards

As illustrated in several other chapters, drug discovery can proceed along a number of different routes that begin with some collection of “surprising observations,” such as in the accidental identification of lithium as a mood-stabilizer or in the isolation of streptomycin and cephalosporin antibiotics from naturally occurring sources. In contrast, a general approach to rational drug design and development begins with the identification of some promising chemical which is then successively modified and tested for effectiveness based on an appropriate animal model. Such a process, for example, led Gerhard Domagk to the first antimicrobial sulfa drug called Prontosil beginning with synthetic azo dyes. It was also the method followed by Paul Ehrlich in modifying and testing against syphilitic rabbits various arsenicals derived from an initial organic substance called

Atoxyl. The obvious key to such a process of rational drug discovery is to identify a promising starting chemical or molecule that can then be subjected to repeated modification and clinical testing.

This particular chapter discusses how in the latter half of the twentieth century several different classes of chemicals were subjected to modification and testing that led to a number of prominent psychotropic (mind-affecting) medicines. These include some of the most heavily prescribed “blockbuster” drugs at the time, such as Miltown, Valium, Thorazine, and various antidepressants. We begin with the development of Miltown (meprobamate) by the Czech pharmacologist, Frank Berger (1913–2008), who worked initially in a laboratory in the United Kingdom and later at Wallace Laboratories in the United States. As is typical, some set of abductively relevant “surprising observations” were first unexpectedly encountered in the use of a particular substance which in turn identified the chemical class that would eventually be modified and tested for psychotropic effects.

The first mass-market anti-anxiety (or anxiolytic) drug introduced into clinical practice was meprobamate (also known as Miltown) as developed by Frank Berger working at the New Jersey-based Wallace Laboratories of Carter Products (known for “Carter’s little liver pills”). The route to Miltown began with Berger being employed by the laboratories of the British Drug Houses to study an antibacterial agent called phenoxetol that was believed to help preserve the molds that produced penicillin. In the course of animal testing for toxicity several of the compounds structurally related to this original ether of phenol, Berger noted a set of “surprising observations” in the animals

being used: “administration of small quantities of these substances to mice, rats, and guinea pigs caused tranquilization, muscular relaxation, and a sleep-like condition from which the animals could be roused.” These observations led Berger directly to the abductive conjecture that members from this class of substances could generally operate as some form of tranquilizer in humans.

One particular substance from the series of derivatives studied by Berger, called mephenesin, had been previously synthesized in the early 1900s. It produced the most intense muscle relaxation effects. When Berger moved to the United States in 1948, mephenesin had just been released by the pharmaceutical firm of E. R. Squibb for clinical use as a muscle relaxant during light anesthesia. It was soon recognized that although mephenesin could relieve tension and anxiety, it also had the serious drawback of a very short duration of action primarily on the spinal cord rather than on supraspinal structures. To overcome this disadvantage, Berger initiated a program of mephenesin modification led by the chemist Bernard Ludwig at the Wallace Laboratories. In May of 1950, meprobamate was synthesized (better known as Miltown, so named for a small town near to where Berger lived). By the late 1950s, meprobamate was the most widely used prescription drug in the United States as well as in many other countries. It was particularly popular in the entertainment community where, for example, *Time* magazine dubbed the well-known entertainer Milton Berle, “Uncle Miltown,” for his promotion of the drug. It was also routinely valorized by the terms “emotional aspirin” or “peace pill.” It wasn’t until another tranquilizer from the benzodiazepine class was introduced, called Valium, that the sales of meprobamate were overtaken.

As a postgraduate student in the early 1930s in Poland, Leo Sternbach had synthesized several dyes that would eventually be identified as benzoxadiazepines. Much later in the 1950s working as a pharmacist and chemist at the Hoffmann-LaRoche research facility in Nutley, New Jersey, and given the recent success of Miltown, Sternbach decided to revisit his old class of chemicals and test whether various modifications might have some pharmacological activity. All of the forty or so modifications Sternbach initially tested were pharmacologically inert. One particular compound, however, that was stabilized differently from the others but not tested at the time was merely put on a shelf and labeled as Ro 5-0690. A few years later during a long overdue laboratory clean-up, Ro 5-0690 was found and belatedly submitted to pharmacological evaluation. Surprisingly, it had similar tranquilizing effects as did meprobamate.<sup>1</sup>

In 1960, Ro 5-0690 was the first anxiolytic benzodiazepine introduced into clinical use with the generic name chlordiazepoxide and a brand name of Librium. Librium was followed by another anxiolytic benzodiazepine called Valium (diazepine) in 1963. Sales of Valium in the United States topped all other drugs from the late 1960s through the 1970s. Although no specific abductive conjecture led to these first benzodiazepine tranquilizers, it was still a very fortuitous event that led to the delayed testing of Ro 5-0690.<sup>2</sup>

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<sup>1</sup>This evaluation was first done with the “cat test,” where after receiving an injection of the substance being evaluated, the cat is picked up and suspended by the nape of its neck. If the cat goes limp, the test is considered positive — as it was in this instance.

<sup>2</sup>Valium’s popularity waned after several well-publicized celebrity cases showed its potential for addiction and abuse (for those old enough to remember, Elizabeth Taylor and Tammy Faye Baker come to mind). Also, a Senate congressional hearing in 1979 led by Edward Kennedy and centered on the problems posed by Valium, eventually led to the loss of the drug’s general appeal to the medical community.



The identification of the first “blockbuster” antipsychotic drug (also known as a “major tranquilizer”) was initiated in France in the early 1950s. Its origins, however, extend back to the late 1800s and to the dye methylene blue of interest to Paul Ehrlich as a pharmaceutically active anti-malarial agent. As it so happens, methylene blue is a phenothiazine derivative which was itself first synthesized in the late 1800s. Phenothiazine was to become the lead chemical from which many of the initial antipsychotic drugs were produced in the 1950s and 60s.

The breakthrough anti-psychotic drug chlorpromazine (CPZ), a derivative of phenothiazine with brand names of Thorazine and Largactil, among others, was synthesized in December of 1951 by the chemist Paul Charpentier in the laboratories of the French pharmaceutical company Rhône-Poulenc. It was released in May of 1952 as a possible potentiator for general anesthesia. The French army surgeon, Henri Laborit (1914–1995), used CPZ as an adjunct to surgical anesthesia and noticed a set of “surprising observations” in the patients so treated – a complete disinterest in one’s surroundings without a loss of consciousness, and with only a minimal tendency to sleep.

Henri Laborit convinced several of his colleagues at the Val de Grâce military hospital in Paris to treat a few of their severely impaired patients with CPZ. The first person to receive CPZ was Jacques Lh., a twenty-four-year-old agitated manic male. After less than a month receiving CPZ the patient was ready “to resume normal life.” More extensive clinical trials were carried out by Pierre Deniker (1917–1998) at Saint-Anne’s hospital in Paris and by Heinz Lehmann (1911–1999) at Montreal’s Douglas Hospital. In 1957, the

prestigious Albert Lasker Award was presented to these three key players in the clinical development of CPZ — Henri Laborit for first considering CPZ as a psychiatric therapeutic agent; Pierre Deniker for his role in introducing CPZ into psychiatry; and Heinz Lehmann for bringing to the medical community in general the significance of CPZ for clinical psychiatric practice.

One of the better examples of drug discovery that occurred by paying attention to a set of “surprising observations” when some substance was being used for another purpose, is in how the antidepressant iproniazid was first identified. In the early 1950s, the two hydrazine chemicals iproniazid and its structural analog isoniazid were being used successfully to treat pulmonary tuberculosis. As a noticeable side effect, many of the mortally ill patients experienced “a great sense of well-being, a return of appetite, and weight gain.” Struck by these “antidepressant” side effects, several investigators turned to the use of iproniazid in non-tuberculosis patients with the explicit purpose of treating severe depression. One of the most prominent of these investigators was Nathan Kline at the Rockland State Hospital in New York. For his efforts in introducing this first monoamine oxidase inhibitor (MAOI) to the wider psychiatric community, Kline received the 1964 Albert Lasker Award “for the introduction and use of iproniazid in the treatment of severe depressions.” Part of this award citation follows:

Dr. Kline more than any other single psychiatrist has been responsible for one of the greatest revolutions ever to occur in the care and treatment of the mentally ill. Literally hundreds of thousands of people are leading productive normal lives, who – but for Dr. Kline’s work – would be leading lives of fruitless despair and frus-

tration. Having pioneered the introduction and use of Rauwolfia and other tranquilizing drugs for the treatment of schizophrenia in 1954, Dr. Kline first reported in 1957 the beneficial effects of iproniazid, a monoamine oxidase inhibitor, in the treatment of severe depression.

His experiments confirmed the euphoric effect of iproniazid first reported in the treatment of tuberculosis. They were undertaken by Dr. Kline and his associates at Rockland State Hospital because the new tranquilizers were not proving useful in the treatment of severe depression. Deteriorated, regressed patients who had been hospitalized for long periods of time, and who had been unresponsive to other treatment, showed an improvement within a five-week period of observation. They became more alert, responsive and sociable. At the same time, more typical depressions treated in Dr. Kline's private practice showed an even more dramatic response to the drug, and thus demonstrated that many patients could be treated on an ambulatory basis and did not need to be hospitalized.

Although iproniazid was one of the first antidepressants to be approved for use in 1958, it was withdrawn in most of the world by 1961 because of a high level of liver toxicity that occurred with its use. Canada withdrew iproniazid a few years later because of its interactions with certain food products containing the common monoamine of tyramine.

The first tricyclic (three-ring) antidepressant (TCA), called imipramine, was also discovered through a set of "surprising observations" that occurred when imipramine was being used for another purpose. In this case, the discoverer was the Swiss psychiatrist, Roland Kuhn, at the psychiatric clinic in Münsterlingen. Because of tight budget concerns, Kuhn had asked the Swiss pharmaceutical firm Geigy if they had any new antipsychotic drugs that he might try out on his schizophrenic

patients. Geigy provided a supply of G22355 (imipramine), a derivative of phenothiazine similar in structure to chlorpromazine which at the time was being used world-wide as an anti-psychotic agent.

Although psychotic symptoms were not relieved in those patients who received imipramine and even got worse in several instances, those patients who were merely depressed did improve remarkably. Kuhn then switched from treating his schizophrenic patients with imipramine to those who were merely depressed. Generally, for most of these patients depressive symptoms cleared up within three weeks.

Although tricyclic antidepressants such as imipramine are still prescribed, they have been largely replaced by the newer SSRI antidepressants (selective serotonin reuptake inhibitors) with brand names such as Lexapro, Paxil, Zoloft, and so on. There is no “surprising” set of observations that led to the identification of the SSRIs but rather dogged rational drug design based on brain chemistry. Against the backdrop of these newer antidepressants is the widespread acceptance that depression is caused by a chemical imbalance that can be rectified by drugs.

There are several excellent book-length sources for how psychopharmacology developed over the twentieth century that the reader may wish to consult for more detail. Here are four of the best:

David Healy (2002). *The Creation of Psychopharmacology*. Harvard University Press, Cambridge.

David Herzberg (2009). *Happy Pills in America, From Miltown to Prozac*. The Johns Hopkins University Press, Baltimore.

Edward Shorter (1997). *A History of Psychiatry, From the Era*

*of the Asylum to the Age of Prozac.* Wiley and Sons, New York.

Edward Shorter (2021). *The Rise and Fall of the Age of Psychopharmacology.* Oxford University Press, New York.

## Part II

# MEDICAL THEORIES FOR WHY SOMETHING OCCURS

## Chapter 15

# Gregor Mendel and the Foundations of Classical Genetics (1856)

I do not believe we can blame genetics for adultery, homosexuality, dishonestly and other character flaws.

— Jerry Falwell (1933–2007)

The founder of the modern science of genetics, Gregor Mendel (1822–1884), was an Austrian-Czech biologist and Augustinian friar at St. Thomas Abbey in Brno, a city now located in the Czech Republic. During the seven-year period from 1856 to 1863, Mendel carried out some thirty thousand breeding experiments in the large garden attached to the Abbey using as a model the simple pea plant with its various dichotomous characteristics. Based on the results from these pea plant experiments, Mendel established several of the general rules of heredity now commonly referred to as the Principles (or Laws) of Mendelian Inheritance.

The pea plants that Mendel used in his breeding experiments could be distinguished through seven dichotomous properties: plant height, pod shape, pod color, seed shape, seed color, flower position, and flower color. Taking seed color (yellow or green) as our prime example

for now, Mendel began with “true-breeding” plants defined as those always producing seeds (peas) of the same yellow or green color when self-pollinated over successive generations. Two sets of “surprising” observations ensued that led to the abductive conjectures that would eventually be restated as the Principles of Mendelian Inheritance:

1) when a pair of true-breeding yellow and green pea plants are cross-bred, only yellow peas result.

2) when the yellow pea plants from (1) self-pollinate, green pea plants reappear in a ratio of three yellow seed plants to one green seed plant (3:1).

The abductive conjecture(s) Mendel formulated to explain these two empirical observations about the seed colors of yellow and green can be phrased as follows: for a trait such as seed color, there is an invisible determining “factor” (now called a “gene”) composed of two “subfactors” (now called “alleles”). Of these two subfactors, one allele comes from each of the two parents. Moreover, an allele can be labeled as “dominant” or “recessive” with respect to the trait being considered. Using Mendel’s notation, suppose the capital letter “A” denotes a yellow (dominant) allele, and the small letter “a” denotes a green (recessive) allele. A true-breeding yellow seed plant has the AA gene, and a true-breeding green seed plant has the aa gene.

The plants resulting from crossing a true-breeding yellow seed plant with a true-breeding green seed plant will all have the allele pair Aa, and because the A allele is dominant, it will be yellow-seeded. In crossing two plants from this last generation all having the allele pair, Aa, there are four possible gene progenies; considering the yellow allele dominant, the colors of the resulting seeds will be



as follows:

AA (yellow)

Aa (yellow)

aA (yellow)

aa (green)

Thus, the ratio of plants with yellow seeds to those with green seeds is 3 to 1.

The empirical ratio of 3 to 1 obtained by Mendel for seed color is mirrored closely by the six other dichotomous traits. Moreover, all seven traits operate independently of each other producing the expected ratios empirically when traits are considered together. For example, consider the seed shapes of round and wrinkled, where “round” is dominant and denoted by B; “wrinkled” is recessive and denoted by b. In considering the (round; yellow) unobserved genotype, BbAa, crossed with another of the same BbAa form, sixteen possible patterns emerge with the four observed phenotype patterns having the ratios 9:3:3:1 –

round; yellow (9)

round; green (3)

wrinkled; yellow (3)

wrinkled; green (1)

These theoretical ratios can then be compared with those empirically produced from actual crosses; generally, the theoretical and empirical ratios are very close.

The notions of dominance/recessiveness and of how traits are determined can be formulated more explicitly as Mendel’s Three Principles of Inheritance:

Principle of Segregation: traits are determined by genes that are composed of two alleles with one allele coming from each of the two parents.

Principle of Dominance: in a pair of alleles comprising a gene, one allele is dominant and masks the expression of the other (recessive) allele.

Principle of Independent Assortment: the inheritance of one characteristic is independent of the inheritance of another characteristic.

Mendel presented a paper summarizing his pea plant breeding experiments in two parts, entitled “Experiments on Plant Hybridization,” This was done at two meetings of the Natural History Society of Brno in February and March of 1865. Although it was then formally published in 1866 by a local journal from Brno, it received little attention at the time. Mendel himself became abbot of the St. Thomas Abbey in 1868 which effectively ended any further scientific work of the depth represented by his 1856 publication.

In the early 1900s Mendel’s work was rediscovered by a number of authors searching for a viable theory of discontinuous inheritance of the same type Mendel had studied with his pea plants. Most efforts at that time had been on “blending inheritance” where traits from each parent are just averaged. So, some twenty years after his death, Mendel achieved a rightful position as “father of modern genetics.” Given Mendel’s emphasis on dominant and recessive alleles, he gave a genotypic view of heredity through unobservable gene patterns rather than one that was solely phenotypic and only based on observable characteristics.

Although Mendel’s Principles provides an initial basis for a modern

theory of inheritance, there are a number of complexities it can't handle; a few of these are listed below:

*linked genes*: when genes are located close to each other on the same chromosome, they tend to be inherited together. This violates the Principle of Independent Assortment.

*codominance*: this occurs when both alleles in a gene are expressed equally such as in the human AB blood type. This violates the Principle of Dominance.

*incomplete dominance*: again violating the Principal of Dominance, incomplete dominance occurs when a mixture of the allele phenotypes is expressed, such as when red and white flowers produce pink progenies.

*polygenic inheritance*: this occurs when a trait is controlled by multiple genes such as in human skin color or height.

Several books detail the life of Gregor Mendel and his work; two of the most comprehensive are:

Robin Marantz Henig (2002). *The Monk in the Garden: The Lost and Found Genius of Gregor Mendel, the Father of Genetics*. Houghton Mifflin Company, New York.

Daniel J. Fairbanks (2022). *Gregor Mendel: His Life and Legacy*. Prometheus Books, Guilford, Connecticut.

## Chapter 16

# The Identification of Cell-Mediated Immunity (1882)

[Metchnikoff is a] hysterical character out of one of Dostoevsky's novels.

— Paul de Kruif (author of *Microbe Hunters*)

Élie Metchnikoff (1845–1916) was a Russian zoologist known for his work on innate or cell-mediated immunity that he carried out during the last several decades of the Nineteenth Century. In the early 1900s, Metchnikoff's interests turned to aging and longevity; he, in fact, coined the term “gerontology” and is generally considered to be the father of the field. Metchnikoff was one of the first advocates for the use of probiotics such as yogurt and other fermented milk products that contain lactic acid and other presumably beneficial bacteria as a way of replacing the harmful organisms that might be present in the large intestine. This type of bacterial replacement supposedly promoted health and longevity, and is part of Metchnikoff's notion of orthobiosis, a term he used to encompass all of the factors that might affect longevity and well-being.

Élie Metchnikoff was born in May of 1845 to a Romanian noble father and a Ukrainian-Jewish mother near the town of Kharkiv

in what is now the present-day Ukraine. After obtaining a degree in the natural sciences from the University of Kharkiv, Metchnikoff completed his doctoral degree in 1867 from the University of Saint Petersburg on the development of the three germ layers in invertebrate embryos: endoderm (the inner layer), ectoderm (the outer layer), and mesoderm (the middle layer). It was in the mesoderm that Metchnikoff first saw the “surprising” mobile cells, later to be called phagocytes, that would form the basis for his abductive hypothesis of cell-mediated immunity (the doctrine of phagocytosis).

Metchnikoff became a Lecturer/Professor at Odessa University in 1867 but left in 1882 because of the political turmoil that surrounded the assassination of Tsar Alexander II. Metchnikoff and his whole extended family, which included his wife and her siblings, went to Sicily to set up a private laboratory in Messina. It was in Messina that Metchnikoff was to have his “epiphany” regarding the abductive conjecture of cell-mediated immunity. Metchnikoff left for Paris in 1888 where he accepted an appointment and eventual directorship at the Pasteur Institute. He remained in Paris for the rest of his life.

Olga Metchnikoff published a biography of her husband in 1921, several years after he had died, with the obvious title: *Life of Elie Metchnikoff* (1845–1916). A short section from this biography is given below (pp. 116–118) that relates to the (abductive) conjecture of cell-mediated immunity as witnessed in transparent starfish larvae. This hypothesis resulted from the “surprising” intracellular digestion seen in the mobile cells of the mesoderm (for example, in engulfing grains of the red-dye pigment of carmine). The extracted section below also mentions the large extrapolation to human immunity made

by Metchnikoff and to the formation of pus through white blood corpuscles, now considered as human analogues for the mobile cells from the mesoderm seen in starfish larvae:

... yet, the mobile cells of the mesoderm preserve their faculty of intracellular digestion. As he studied these phenomena more closely, he ascertained that mesodermic cells accumulated around grains of carmine introduced into the organism.

All this prepared the ground for the phagocyte theory, of which he himself described the inception in the following words:

I was resting from the shock of the events which provoked my resignation from the University and indulging enthusiastically in researches in the splendid setting of the Straits of Messina.

One day when the whole family had gone to a circus to see some extraordinary performing apes, I remained alone with my microscope, observing the life in the mobile cells of a transparent star-fish larva, when a new thought suddenly flashed across my brain. It struck me that similar cells might serve in the defence of the organism against intruders. Feeling that there was in this something of surpassing interest, I felt so excited that I began striding up and down the room and even went to the seashore in order to collect my thoughts.

I said to myself that, if my supposition was true, a splinter introduced into the body of a star-fish larva, devoid of blood-vessels or of a nervous system, should soon be surrounded by mobile cells as is to be observed in a man who runs a splinter into his finger. This was no sooner said than done.

There was a small garden to our dwelling, in which we had a few days previously organised a "Christmas tree" for the children on a little tangerine tree; I fetched from it a few rose thorns and introduced them at once under the skin of some beautiful star-fish larvae as transparent as water.

I was too excited to sleep that night in the expectation of the result of my experiment, and very early the next morning I ascertained that it had fully succeeded.

That experiment formed the basis of the phagocyte theory, to the development of which I devoted the next twenty-five years of my life.

This very simple experiment struck Metchnikoff by its intimate similarity with the phenomenon which takes place in the formation of pus, the diapedesis<sup>1</sup> of inflammation in man and the higher animals. The white blood corpuscles, or leucocytes, which constitute pus, are mobile mesodermic cells. But, while with higher animals the phenomenon is complicated by the existence of blood-vessels and a nervous system, in a star-fish larva, devoid of those organs, the same phenomenon is reduced to the accumulation of mobile cells around the splinter. This proves that the essence of inflammation consists in the reaction of the mobile cells, whilst vascular and nervous intervention has but a secondary significance. Therefore, if the phenomenon is considered in its simplest expression, inflammation is merely a reaction of the mesodermic cells against an external agent.

Metchnikoff then reasoned as follows: In man, microbes are usually the cause which provokes inflammation; therefore it is against those intruders that the mobile mesodermic cells have to strive. These mobile cells must destroy the microbes by digesting them and thus bring about a cure.

Inflammation is thus a curative reaction of the organism, and morbid symptoms are no other than the signs of the struggle between the mesodermic cells and the microbes.

In order to verify these conjectures, he started studying the englobing of microbes by mesodermic cells in larvae and in other marine invertebrates which he inoculated [such as in transparent water-fleas and the enclosure of fungal spores having a needle-like shape].

The revolutionary hypothesis proposed by Mechnikoff was simply this: in all living beings, including humans, mobile cells eat up microbes giving the organism immunity against disease. These mobile cells are thus responsible for the healing power of an organism. The abductive conjecture of an innate or cell-mediated immunity could be contrasted with adaptive or humoral immunity which considers various kinds of antibody substances to be present in blood serum

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<sup>1</sup>Defined as the passage of blood cells through the intact walls of the capillaries that typically accompanies inflammation.

and responsible for an organism's immunity to disease. As might have been expected, both types of immunity are generally operative in animals, although it took many years for that conclusion to be generally accepted.

In recognition of a unifying framework for immunity, Élie Mechnikoff and Paul Ehrlich shared the 1908 Nobel Prize in Physiology or Medicine for their separate work on cell-mediated and humoral immunity. The separate Nobel citations for Mechnikoff and Ehrlich are given below:

Mechnikoff: During the second half of the 19th century, it was clear that many diseases are caused by attacks of microorganisms. It was also determined that our immune system protects us against these attacks. Ilya Mechnikov contributed in several ways to our understanding of how this happens. After studies of starfish larvae, in 1882 he pointed to phagocytosis as one of the immune system's ways of operating. By this he meant that certain cells in the blood, white blood cells, work by encapsulating and destroying harmful bacteria and other microorganisms.

Ehrlich: Our immune system protects us from attacks by microorganisms. As part of its defenses, the immune system forms antibodies in the blood that neutralize poisons, or toxins, that are formed by bacteria. One of Paul Ehrlich's contributions to immunology was the transfer of blood serum with antibodies to treat and counteract diphtheria, which he carried out with Emil von Behring. Ehrlich speculated that cells have a kind of receptor that binds to the harmful substances. The receiving elements are knocked off of the cell and become antibodies.

Besides being a founder of the field of modern immunology, Mechnikoff is also considered the father of gerontology. He conjectured that various phagocytic cells which actively defended a host body against pathogens and disease earlier in its life cycle eventually became detrimental later in life, curtailing what he considered was a



more normal life span that extended well past one-hundred years. To achieve this type of longevity, the “bad” bacteria present primarily in the large intestine had to be replaced by life enhancing “good” bacteria. He identified these beneficial bacteria as being present in fermented milk products such as yogurt.

Metchnikoff considered aging to be a disease that could be treated like any other. With this view, he echoed Hippocrates who had declared some 2000 years earlier that “death sits in the bowels” and “bad digestion is the root of all evil.” The toxins from the bacterial putrefaction process generated in the large intestine and released into the circulation are one main cause of aging. Metchnikoff’s general assessment of the utility of the large intestine is stated well in his book, *The Nature of Man; Studies in Optimistic Philosophy* (1903; pp. 72–73):

In the legacy acquired by man from his animal ancestors, there occur not only rudimentary organs that are useless or harmful, but fully developed organs equally useless. The large intestine must be regarded as one of the organs possessed by man and yet harmful to his health and his life. The large intestine is the reservoir of the waste of the digestive processes, and this waste stagnates long enough to putrefy. The products of putrefaction are harmful. When fecal matter is allowed to remain in the intestine, as in cases of constipation, a common complaint, certain products are absorbed by the organism and produce poisoning, often of a serious nature. Every one knows that a high temperature may be the result of constipation in women after childbirth, or in patients recovering from an operation. This is due to an absorption of substances produced by the microbes of the large intestine. Similar products may be the cause of an attack of acne or of other skin diseases. In time, the presence of a large intestine in the human body is the cause of a series of misfortunes.

As mentioned earlier, a second major determinant of aging for Metch-

nikoff were the phagocytes that earlier in one's life performed necessary healthy maintenance and defined the basis for innate immunity. In the elderly, however, cells of the brain and within the body more generally also were consumed causing an overall deterioration of tissue in old age.

Although probiotics and related fermented products are now considered important in maintaining a healthy human microbiome, Metchnikoff came to this view based on what can be labeled charitably as an abductive conjecture. Metchnikoff noted two “surprising” things: first, Bulgarian peasants generally lived relatively long lives and had many centenarians present among the elderly. And secondly, the major component of a Bulgarian peasant's diet was a form of fermented milk or yogurt based on the *Lactobacillus bulgaricus*. From these two “surprising” observations, Metchnikoff drew the conclusion that aging and senility could be mitigated by replacing the toxic bacteria in the intestinal flora by the lactic acids and beneficial bacteria present in fermented and sour milk products.

Metchnikoff drank sour milk every day, following the recommendations he made in his book, *The Prolongation of Life: Optimistic Studies*. He later espoused the potential life-extending properties of lactic acids that could prevent intestinal putrefaction. Metchnikoff died in Paris at the age of 71 from heart failure. He had hoped to live much longer to give some credence to his conjecture of a *death instinct*: by engaging in the beneficial practice of probiotics, his lifespan would be extended to a length where he would just wish an easy death much as one wished to sleep when overly tired.

Many of the abductive hypotheses that Metchnikoff entertained

and which were based on what he considered to be relevant “surprising observations,” seem much more akin to the idiomatic phrase of “jumping to conclusions” rather than to any justifiable formation of a scientific conjecture that could then be studied further through experimentation and/or observation. Or, stated in another way, Metchnikoff seemed to a believer in an adage of “if it could be, it is.”

There are many such premature conclusions that can be identified over the course of Metchnikoff’s research career starting with the immediate extrapolation of what he saw in starfish larva to white blood cells being the main mechanism for innate immunity in humans. Metchnikoff was a true believer in the theory of intestinal auto-intoxication and based this view on many dubious sources of information. For example, Metchnikoff noted that animals with no or a short large intestine seemed to live relatively longer; or, in an Argentinean study that involved calves suffering from a certain intestinal infection, the animals were found to develop severe hardening of the arteries, a sure sign of old age. In another such dubious connection, Metchnikoff was convinced that the once beneficial human phagocytes eventually turned on the host and were partially responsible for the aging process by, for example, eating pigments and allowing for the graying of hair, and generally producing a hardening of the arteries through the toxins they released. As witnessed by the Bulgarian peasants drinking fermented milk products, such “bad” bacteria present in the flora of the gut had to be replaced by beneficial organisms to mitigate aging.

For two relatively recent and complete biographies of Metchnikoff, the reader is referred to *Immunity: How Elie Metchnikoff Changed*

*the Course of Modern Medicine*, by Luba Vikhanski (2016; Chicago Review Press, Chicago, Illinois), and *Metchnikoff and the Origins of Immunology: From Metaphor to Theory*, by Alfred I. Tauber and Leon Chernyak (1991; Oxford University Press, New York).

## Chapter 17

# How Viruses Were Discovered (1890s and later)

[A virus is] simply a piece of bad news wrapped up in protein.

— Peter Medawar (1977)

As briefly discussed in the larger companion volume, one device that Louis Pasteur used to support his germ theory of disease was the unglazed porcelain filter patented by his colleague Charles Chamberland (1851–1908). So, for example, the clear filtrate resulting from an anthrax bacillus culture that was passed through a Chamberland filter could not reproduce the disease in test animals although the bacilli retained by the filter could. Viruses are generally so small that they can pass easily through the pores of a porcelain filter, resulting in a clear filtrate that is still infective. This “surprising” observation was the key to the basic abductive conjecture of some new form of infectious agent, and eventually to the origin of the new term of a “filterable virus.”<sup>1</sup>

There are three individuals working in the last decade of the Nine-

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<sup>1</sup>One particular comprehensive source on viruses and much of their history is Teri Shors, *Understanding Viruses* (Third Edition, 2017). Also, see Alice Lustig and Arnold J. Levine, *Minireview: One Hundred Years of Virology*, *Journal of Virology*, 66, 1992, 4629–4631.

teenth Century that are generally considered the pioneers in the discovery of viruses: Adolf Mayer (1843–1942); Dmitri Ivanovsky (1864–1920); and Martinus Beijerinck (1851–1931). Adolf Mayer was a German agricultural biologist working as the director of the Agricultural Experiment Station at Wageningen in the Netherlands when he was asked by a group of Dutch farmers in 1879 to study a disease adversely affecting their tobacco plants. He later (1886) named the malady the “mosaic disease of tobacco.” Mayer was able to demonstrate the “surprising” fact that sap obtained from an affected tobacco plant could be used to infect another one that was initially healthy. Although Mayer could not culture or even see an actual infecting agent through the microscopes then available, he still (abductively) conjectured that the transmitting agent must be some type of bacteria. It would take the other two named pioneers to show that the infecting agent could pass through the pores of a Chamberland filter, and thus was not the usual type of visible bacterial entity.

Dmitri Ivanovsky was a Russian botanist sent to the Ukraine and Crimea to study the same tobacco disease investigated by Adolf Mayer which was then causing great harm on the plantations located in these two areas. In both places he discovered that the tobacco disease was caused by an entity that could pass through a Chamberland filter but was much too small to be seen under a microscope. Ivanovsky published his findings in 1892, establishing his status of being considered at least a co-discoverer of viruses and one of the founders of the field of virology.

In 1898, the Dutch microbiologist Martinus Beijerinck, working within the Wageningen Agricultural School, as did his predecessor

Adolf Mayer, and later at Delft Polytechnic, replicated Ivanovsky's experiments independently. He later acknowledged Ivanovsky's priority in the discovery of a filterable submicroscopic entity causing the tobacco mosaic disease, and which would eventually be called the tobacco mosaic virus (TMV). It was the first "filterable virus" to be studied in depth during the first half of the Twentieth Century. Consistent with the experiments of Ivanovsky and Mayer, Beijerinck could not culture the filterable infectious material, and contrary to the agent being a bacterial spore, heating the filtrate to ninety degrees Celsius destroyed its ability of infect healthy plants. Also, the infectious entity was impervious to antibacterial substances such as alcohol and formalin (formaldehyde) at doses known to kill other microbes. Given the evidence, Beijerinck concluded correctly that whatever the disease entity was, it could replicate and multiply only within living cells. Beijerinck named the new pathogen a "virus," and indicated that it was somewhat liquid and called it a *contagium vivum fluidum* (a contagious living fluid). Quoting from a translation of Beijerinck's 1898 report:

There appears to be little doubt that the contagium must be regarded as liquid, or perhaps better expressed, as water-soluble. Hence it might conceivably serve as an explanation that the contagium, in order to reproduce, must be incorporated into the living protoplasm of the cell, into whose reproduction it is, in a manner of speaking, passively drawn.

In the late 1800s, two German bacteriologists, Friedrich Loeffler (1852–1915) and Paul Frosch (1860–1928), extended the notion of a "filterable virus" to the animal disease called foot-and-mouth. The work done by Loeffler and Frosch was carried out as part of a commission formed in 1897 under Robert Koch, then heading the newly

formed Prussian Institute for Infectious Diseases in Berlin. For this study of foot-and-mouth disease, Loeffler and Frosch are also considered among the founders of the field of virology for this discovery of the first infectious disease in animals caused by a virus. They considered the infectious agent not to be a liquid but a tiny particle, and demonstrated that a sufficiently heated filtrate which destroyed its infectivity could still then serve as a vaccine protective against the disease itself.

Although significant work on a number of viruses and the diseases they produced (yellow fever, polio, smallpox, and many more) continued unabated throughout the Twentieth Century, TMV nevertheless remained a prototypic virus for study. In 1935, for example, Wendell Stanley (1904–1971) was able to produce a crystallization of TMV, bringing the virus into the world of the chemists and the 1941 Nobel Prize in Chemistry to Stanley. Further work with TMV showed its makeup to be components of protein and genetic material (ribonucleic acid or RNA), the latter being the “bad news” in the Medawar quote given at the beginning of this chapter. Pictures of TMV followed using the electron microscope in the late 1930s to finally make a filterable virus visible to the human eye.

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A “bacteriophage” is a virus that infects and replicates itself within bacteria, typically destroying the latter in the process. The term, often shortened to just “phage,” is derived from “bacteria” and the Greek word “phagein” which means to “devour” or “eat.” A phage only replicates after the injection of its DNA or RNA genome into



the cytoplasm of a bacterium. The latter is then destroyed when the newly replicated phages force a cell wall to burst, thus releasing the phages into the surrounding environment. At present, especially in the former Soviet Union and Central Europe more generally, phages are seen as a possible alternative therapeutic mechanism against strains of bacteria that may have become multi-drug resistant.<sup>2</sup>

The early identification of phages and their behavior will be discussed chronologically through the three individuals generally considered most responsible for their initial discovery: Ernest Hankin (1865–1939); Frederick Twort (1877–1950); and Felix d’Herelle (1873–1949). These individuals all witnessed some set of “surprising” observations that could be explained by conjecturing the existence of small infective agents that were invisible with the microscopes then available but which could pass through a Chamberland filter and still destroy a particular bacterial organism.

Ernest Hankin was an English microbiologist sent to India in 1892 to study cholera and other infectious diseases endemic in various parts of the British Empire. He conducted a series of tests on water taken from the Ganges and Jamuna rivers and found something very “surprising”: water from both rivers seemed to have a type of antibiotic effect, with the ability to kill cultures of the water-borne bacteria that causes cholera. Hankin published his observations in the *Annals of the Pasteur Institute* in 1896 under the (translated) title: “The bactericidal action of the waters of the Jamuna and Ganges

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<sup>2</sup>A particularly good source for the past history of phages and their current status is the 2023 text by Tom Ireland, *The Good Virus: The Amazing Story and Forgotten Promise of the Phage* (W. W. Norton & Company, New York).

rivers on Cholera microbes.” This publication was arguably the first to describe in print what was most likely the action of phages. In Mark Twain’s (1897), *Following the Equator: A Journey Around the World*, there is a section devoted to the bactericidal action of the waters of the Ganges, and which mentions the work of Hankin by name. This short section follows:

But I should get tired of seeing them wash their mouths with that dreadful water and drink it. In fact, I did get tired of it, and very early, too. At one place where we halted for a while, the foul gush from a sewer was making the water turbid and murky all around, and there was a random corpse slopping around in it that had floated down from up country. Ten steps below that place stood a crowd of men, women, and comely young maidens waist deep in the water – and they were scooping it up in their hands and drinking it. Faith can certainly do wonders, and this is an instance of it. Those people were not drinking that fearful stuff to assuage thirst, but in order to purify their souls and the interior of their bodies. According to their creed, the Ganges water makes everything pure that it touches – instantly and utterly pure. The sewer water was not an offence to them, the corpse did not revolt them; the sacred water had touched both, and both were now snow-pure, and could defile no one. The memory of that sight will always stay by me; but not by request.

A word further concerning the nasty but all-purifying Ganges water. When we went to Agra, by and by, we happened there just in time to be in at the birth of a marvel – a memorable scientific discovery – the discovery that in certain ways the foul and derided Ganges water is the most puissant [powerful] purifier in the world! This curious fact, as I have said, had just been added to the treasury of modern science. It had long been noted as a strange thing that while Benares is often afflicted with the cholera she does not spread it beyond her borders. This could not be accounted for. Mr. Henkin, the scientist in the employ of the government of Agra, concluded

to examine the water. He went to Benares and made his tests. He got water at the mouths of the sewers where they empty into the river at the bathing ghats [steps]; a cubic centimetre of it contained millions of germs; at the end of six hours they were all dead. He caught a floating corpse, towed it to the shore, and from beside it he dipped up water that was swarming with cholera germs; at the end of six hours they were all dead. He added swarm after swarm of cholera germs to this water; within the six hours they always died, to the last sample. Repeatedly, he took pure well water which was barren of animal life, and put into it a few cholera germs; they always began to propagate at once, and always within six hours they swarmed—and were numberable by millions upon millions.

For ages and ages the Hindoos [sic] have had absolute faith that the water of the Ganges was absolutely pure, could not be defiled by any contact whatsoever, and infallibly made pure and clean whatsoever thing touched it. They still believe it, and that is why they bathe in it and drink it, caring nothing for its seeming filthiness and the floating corpses. The Hindoos [sic] have been laughed at, these many generations, but the laughter will need to modify itself a little from now on. How did they find out the water's secret in those ancient ages? Had they germ-scientists then? We do not know. We only know that they had a civilization long before we emerged from savagery. ...

The second bacteriophage pioneer, Frederick Twort, was an English bacteriologist who in 1914 set out to grow *in vitro* the vaccinia virus that produces cowpox. At the time, all smallpox vaccines were made in the skin of calves, and were invariably contaminated with bacteria from the genus *Staphylococcus*. Twort plated some of the smallpox vaccine on nutrient agar, producing large *Staphylococci* colonies. But “surprisingly,” these bacterial colonies contained minute glassy areas (later called viral plaques) visible with a magni-

ying glass. When subcultured, these plaques would not grow which led Twort to conjecture that these glassy areas resulted from the destruction of bacterial cells. He was also able to move these areas repeatedly to other *Staphylococci* colonies, generating more bacterial destruction in the new media. Whatever the agent was, it could pass through a porcelain filter and required the bacterial colonies for its own growth. Twort published his observations in *The Lancet* in 1915, and called the glassy plaques he identified a bacteriolytic agent capable of destroying bacterial cells.

The third and most prominent pioneer in the study of bacteriophages is Felix d’Herelle, a self-taught French-Canadian microbiologist who a few years after Twort’s seminal publication discovered and actually named bacteriophages independently. Working as an unpaid laboratory assistant at the Pasteur Institute in Paris, d’Herelle was sent in 1915 to study an outbreak of dysentery among a group of French troops stationed on the outskirts of Paris. After collecting a substantial amount of diarrheal output from both affected and recovering soldiers, d’Herelle returned to the Pasteur labs. Over the next year he passed various amounts of the soldiers’ material through a porcelain filter, and added the clear filtrate to agar plates growing colonies of *Shigella*, a major contagious cause of dysentery. Much as did Twort, d’Herelle obtained the same type of “surprising” glassy spots in his bacterial cultures, denoting areas of destroyed bacteria.

The first results of d’Herelle’s dysentery study were presented to the French Academy of Sciences on September 3, 1917, in a paper entitled, “On an invisible microbe antagonistic toward dysenteric bacilli: brief note by Mr. F. D’Herelle, presented by Mr. Roux.” A

translated first paragraph for this short paper follows:

I have isolated, from stools and, in one case, from the urine of patients recovering from bacillary dysentery, an invisible microbe endowed with antagonistic effects toward the Shiga [Shigella] bacillus. It is particularly easy to isolate in the case of common enteritis following dysentery. In convalescing patients who do not have this complication, the anti-Shiga microbe disappears very rapidly following the disappearance of the pathogenic bacillus. Despite numerous attempts, I have never found antagonistic microbes either in the stools of dysenteric patients who are still contaminated or in the stools of normal healthy subjects.

Over the next few decades, d'Herelle discovered other phages that could infect and kill a number of important bacterial types including typhoid and cholera. Much of d'Herelle's later work was published in his translated text, *The Bacteriophage: Its Role in Immunity* (1923).<sup>3</sup> From a literary perspective there is even the novel, *Arrowsmith*, written by Sinclair Lewis (aided by Paul DeKruif), and winner of the 1926 Pulitzer Prize which was declined by Lewis. In the novel, Martin Arrowsmith, a fictional doctor/researcher identified phages through their viral plaques, but is later informed about d'Herelle's priority of discovery. A few of the relevant paragraphs from the novel follow:

That morning Martin had isolated a new strain of staphylococcus bacteria from the gluteal carbuncle of a patient in the Lower Manhattan Hospital, a carbuncle which was healing with unusual rapidity. He had placed a bit of the pus in broth and incubated

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<sup>3</sup>The reader is also referred to d'Herelle's 1999 biography by William C. Summers, *Félix d'Herelle and the Origins of Molecular Biology*, Yale University Press, New Haven.

it. In eight hours a good growth of bacteria had appeared. Before going wearily home he had returned the flask to the incubator.

... he absent-mindedly wavered to the incubator, and found that the flask, in which there should have been a perceptible cloudy growth, had no longer any signs of bacteria – of staphylococci.

“Now what the hell” he cried. “Why, the broth’s as clear as when I seeded it! Now what the – Think of this fool accident coming up just when I was going to start something new!”

He hastened from the incubator, in a closet off the corridor, to his laboratory and, holding the flask under a strong light, made certain that he had seen aright. He fretfully prepared a slide from the flask contents and examined it under the microscope. He discovered nothing but shadows of what had been bacteria: thin outlines, the form still there but the cell substance gone; minute skeletons on an infinitesimal battlefield.

He raised his head from the microscope, rubbed his tired eyes, reflectively rubbed his neck – his blouse was off, his collar on the floor, his shirt open at the throat. He considered:

“Something funny here. This culture was growing all right, and now it’s committed suicide. Never heard of bugs doing that before. I’ve hit something! What caused it? Some chemical change? Something organic?”

...

A detective, hunting the murderer of bacteria, he stood with his head back, scratching his chin, scratching his memory for like cases of microorganisms committing suicide or being slain without perceptible cause. He rushed up-stairs to the library, consulted the American and English authorities and, laboriously, the French and German. He found nothing.

...

There was a cloudy appearance of bacteria in all the flasks except those in which he had used broth from the original alarming flask. In these, the mysterious murderer of germs had prevented the growth of the new bacteria which he had introduced.

...

“I have observed a principle, which I shall temporarily call the X Principle, in pus from a staphylococcus infection, which checks the growth of several strains of staphylococcus, and which dissolves the staphylococci from the pus in question.”

...

“What is this mysterious discovery you’re making, Arrowsmith? I’ve asked Dr. Gottlieb, but he evades me; he says you want to be sure, first. I must know about it, not only because I take a very friendly interest in your work but because I am, after all, your Director!”

Martin felt that his one ewe lamb was being snatched from him but he could see no way to refuse. He brought out his note-books and the agar slants with their dissolved patches of bacilli. Tubbs gasped, assaulted his whiskers, did a moment of impressive thinking, and clamored:

“Do you mean to say you think you’ve discovered an infectious disease of bacteria, and you haven’t told me about it? My dear boy, I don’t believe you quite realize that you may have hit on the supreme way to kill pathogenic bacteria ... And you didn’t tell me!”

“Well, sir, I wanted to make certain –”

“I admire your caution, but you must understand, Martin, that the basic aim of this Institution is the conquest of disease, not making pretty scientific notes! You may have hit on one of the discoveries of a generation; the sort of thing that Mr. McGurk and I are looking for ... ”

...

Gottlieb ambled toward him. “It iss a pity, Martin, but you are not the discoverer of the X Principle.”

“Wh - what – ”

“Someone else has done it.”

“They have not! I’ve searched all the literature, and except for Twort, not one person has even hinted at anticipating – Why, good Lord, Dr. Gottlieb, it would mean that all I’ve done, all these weeks,

has just been waste, and I'm a fool — ”

“Vell. Anyvay. D'Herelle of the Pasteur Institute has just now published in the Comptes Rendus, Academie des Sciences, a report – it is your X Principle, absolute. Only he calls it ‘bacteriophage.’ So.”

...

\* \* \*

This chapter on viruses will end with parts of an obituary from the *New York Times* (March 8, 2024) for Anthony Epstein who co-discovered in 1964 the ubiquitous Epstein-Barr virus (EBV), the first virus shown to cause cancer in humans. It is estimated that over ninety per cent of all humans carry EBV latently, most likely transmitted from some initial salivary source, possibly maternal or from a bout of “kissing disease” (also known as glandular fever, mononucleosis, or “mono”). There are two salient instances of abductive reasoning mentioned in the obituary. One derives from Epstein hearing Denis Burkitt discuss a “surprising” geographical pattern of large facial tumors in Ugandan children, now called Burkitt’s Lymphoma. Epstein conjectured that a virus was the cause and proceeded, albeit unsuccessfully at first, to search for it in tumor samples sent to London from Uganda. A second “surprising” observation was the presence of floating tumor cells that occurred in one of the Ugandan samples that was delayed in transit. Epstein was actually able to culture the tumor cells that were present, and conjectured correctly that these cells harbored EBV and allowed it to reproduce. As they say, the rest is history!



## **Dr. Anthony Epstein, Pathologist Who Discovered Epstein-Barr Virus, Dies at 102**

**By Delthia Ricks**

His groundbreaking research, which he performed with Yvonne Barr, his doctoral student, uncovered the first virus capable of causing cancer in humans.

In March 1961, Dr. Anthony Epstein, a pathologist at Middlesex Hospital in London, almost skipped a visiting physician's afternoon lecture about children with exceptionally large facial tumors in Uganda.

The physician, Dr. Denis Burkitt, a native of Ireland who called himself a bush surgeon, showed slides of bulbous tumors [later to be called Burkitt's Lymphoma] that emerged along the jawline and occurred in tropical African regions where rainfall was high. During his lecture, Dr. Burkitt mapped a veritable pediatric cancer belt that extended across equatorial Africa.

Despite Dr. Epstein's initial reluctance to attend the talk — he sat in the rear so he could make a quick escape — his excitement grew the longer Dr. Burkitt spoke. By the time the lecture was over, he knew that he would drop all of his ongoing projects to find the cause of that unusual malignancy. His doctoral student, Yvonne Barr, soon joined him and, by 1964, their groundbreaking research had uncovered the first virus capable of causing cancer in humans.

He rocked the scientific world with the announcement. Some physicians and scientists applauded the discovery; others refused to accept it.

Dr. Epstein died on Feb. 6 at his home in London. He was 102. His death was confirmed by the University of Bristol, where he was a professor of pathology from 1968 to 1985, and where he had served as the head of the department for 15 years.

The pathogen that came to bear his and Dr. Barr's names — Epstein-Barr virus — belongs to the herpes family and is one of the most ubiquitous on the planet. An estimated 90 percent of the world's adult population carries the virus, which is also known as

E.B.V.

“To have the insight and to be able to follow his hypothesis, with a little acknowledged serendipity, and identify the novel virus was pioneering,” Dr. Darryl Hill, who heads the University of Bristol’s School of Cellular and Molecular Medicine in England, said in an email.

Studies since Dr. Epstein’s discovery have linked E.B.V., which is spread through close human contact, to many medical conditions, including multiple sclerosis and long Covid. As with other members of the herpes family, once infected with the virus, a person is infected for life.

“Most people never know they’re infected,” Jeffrey Cohen, the chief of the Laboratory of Infectious Diseases at the National Institute of Allergy and Infectious Diseases, told *The New York Times* in 2022.

E.B.V. is the cause of mononucleosis, the so-called kissing disease, which primarily afflicts teenagers and young adults with a fever and swollen lymph nodes. It is also associated with Hodgkin’s lymphoma and a nose-and-throat cancer common in China.

The tumor that affects children in Africa, known as Burkitt lymphoma, has also been diagnosed in other tropical regions, such as Brazil and New Guinea. Medical scientists theorize that E.B.V. causes pediatric lymphomas in tropical zones because children in such areas often have weakened immunity from exposure to malaria parasites. The World Health Organization estimates that there are three to six cases of Burkitt lymphoma per 100,000 children annually in endemic regions.

When the 50th anniversary of E.B.V.’s discovery was celebrated in 2014, Dr. Epstein told an interviewer with the BBC what he had been thinking as he listened to Dr. Burkitt speak in 1961.

“I thought there must be some biological agent involved,” Dr. Epstein said. “I was working on chicken viruses which cause cancer. I had virus-inducing tumors at the front of my head.”

The chicken virus he was referring to was Rous sarcoma virus,

the first cancer-causing virus to be discovered, in 1911 by Dr. Francis Peyton Rous, a pathologist at Rockefeller University in New York. Dr. Rous won the 1966 Nobel Prize in Physiology or Medicine. Although a Nobel eluded Dr. Epstein and Dr. Barr, their discovery has had a lasting impact on science and medicine.

“We now know of several viruses and bacterial species that are able to cause certain types of cancer,” Dr. Hill said. “However, one could argue that the Epstein-Barr virus discovery paved the way for some cancers to be preventable by vaccination.”

Vaccines are available against human papillomavirus, or HPV, which causes cervical and other forms of cancer. The hepatitis B vaccine helps to thwart liver cancer. But there is no vaccine against Epstein-Barr, though two candidate vaccines are in early-phase clinical research.

The discovery of the virus was not quick. Dr. Burkitt sent tumor biopsies to London from Kampala, Uganda, but Dr. Epstein couldn't find viruses in the early specimens, according to Dr. Hill, who wrote a remembrance of Dr. Epstein for the University of Bristol.

When another biopsy shipment was diverted from Heathrow Airport to another airport, in Manchester, England, because of fog, the sample seemed doomed, Dr. Hill said.

“By the time the sample reached Tony, it had gone cloudy — usually a sign of bacterial contamination that would consign it to the bin,” Dr. Hill wrote in his tribute. “Tony did not throw it away but examined it carefully

“He discovered, to his surprise, that the cloudiness was due to lymphoid tumor cells that had been shaken off the biopsy in transit and were now floating merrily in suspension.” He continued, “Tony exploited this chance finding to grow cell lines, derived from the tumor, in culture. He showed that these stayed alive indefinitely.”

Studying his new sample with a powerful electron microscope, Dr. Epstein was able to spot the distinct viral signature of a herpes virus. Dr. Hill called the discovery a eureka moment.

Dr. Epstein, Dr. Barr and Dr. Bert Achong, who prepared the specimens for electron microscopy, announced the discovery in a scientific paper published in the March 1964 issue of the scientific journal *The Lancet*.<sup>4</sup>

Dr. Barr died at age 83 in 2016.

Michael Anthony Epstein was born on May 18, 1921, in London and was educated at Trinity College of the University of Cambridge. He was a graduate of Middlesex Hospital Medical School, according to Wolfson College at the University of Oxford.

After leaving the University of Bristol in 1985, Dr. Epstein became a fellow at Wolfson College and remained at the institution until he retired in 2001. He was knighted by Queen Elizabeth II in 1991.

His marriage to Lisbeth Knight ended in divorce in the 1960s. Survivors include his longtime partner, Dr. Katherine Ward, a virologist; two sons from his marriage, Michael and Simon; and a daughter, Susan Holmes.

Dr. Epstein told the BBC in 2014 that one of his most ardent wishes was the development of a vaccine against E.B.V. His wish may come true in the not-too-distant future if current research prevails.

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<sup>4</sup>The title of the *Lancet* paper is “Virus particles in cultured lymphoblasts from Burkitt’s lymphoma.”

## Chapter 18

# Viruses as Causative Agents in the Development of Cancer (Early to Middle Twentieth Century)

If we were to eliminate from science all the great discoveries that had come about as the result of mistaken hypotheses or fluky experimental data, we would be lacking half of what we now know (or think we know).

— Nathan Kline (1916–1983)

This chapter again emphasizes viruses but now concentrates on how they might relate to various forms of cancer or sarcoma in humans and other animals. Although it is now known that viral agents can cause a variety of different cancers (for example, the Epstein-Barr virus and Burkitt's lymphoma; hepatitis B and C and connections to liver cancer; the human herpes type 8 virus and Kaposi's sarcoma, and so on), the paths to these realizations were not always straightforward. Here, the emphasis will be on four individuals and how some prescient abductive conjecturing from various sets of "surprising observations" led to our current understanding of possible viral causes for certain types of cancer:

Peyton Rous (1879–1970) discovered in 1911 that a chicken tumor

was caused by a transmittable virus, later named the Rous sarcoma virus (RSV);

George Papanicolaou (1883–1962) developed the ubiquitous Pap (smear) test in the 1920s for the early screening for uterine cancer;

Baruch Blumberg (1923–2011) identified the hepatitis B virus which we now know can lead to liver cancer. He also helped develop a diagnostic test for hepatitis B and a vaccine for its prevention.

Harald zur Hausen (1936–2023) discovered the role human papilloma viruses (HPV) play in cervical cancer. In turn, this recognition has led to the recent introduction of vaccines against cervical cancer that are typically given to young teenagers before the age when they might first engage in sexual activity.

\* \* \*

We begin with Peyton Rous, and a woman who early in 1910 brought a Plymouth Rock hen into the Rockefeller Institute for Medical Research that had developed a “large irregularly globular mass” on its left breast. Rous identified the growth as a “spindle-celled sarcoma.” He was then able to transmit tumors of the same type to healthy chickens within the same breed using cell-free filtrates of the tumor where all solid material had been removed. This “surprising observation” of the clear filtrate’s ability to serially reproduce the tumors, led directly to the abductive conjecture of a viral cause for the sarcoma, and to what is now generally referred to as an oncovirus.

The first major article by Peyton Rous reporting on his chicken experiments appeared in the *Journal of Experimental Medicine* in 1911, with the title: “A Sarcoma of the Fowl Transmissible By an

Agent Separable From the Tumor Cells.” Note the care that Rous takes in avoiding the term “virus” in the article’s opening paragraph reproduced below:

A transmissible sarcoma of the chicken has been under observation in this laboratory for the past fourteen months, and it has assumed of late a special interest because of its extreme malignancy and a tendency to wide-spread metastasis. In a careful study of the growth, tests have been made to determine whether it can be transmitted by a filtrate free of the tumor cells. Attempts to so transmit rat, mouse, and dog tumors have never succeeded; and it was supposed that the sarcoma of the fowl would not differ from them in this regard, since it is a typical neoplasm [tumor]. On the contrary, small quantities of a cell-free filtrate have sufficed to transmit the growth to susceptible fowls.

Peyton Rous died in 1970 not long after he received the Nobel Prize in 1966, some 55 years after his discovery of a viral cause for what is now known as the Rous sarcoma. To this day he remains the oldest recipient of the Nobel Prize in Medicine or Physiology. The beginning part of a long obituary by Jane Brody in the *New York Times* (February 17, 1970) is given below:

Dr. Peyton Rous, who 60 years ago demonstrated for the first time that animal cancer can be caused by a virus, died of cancer early yesterday at Memorial Hospital in New York. He was 90 years old.

In 1966, he received what many fellow scientists thought was a long-overdue Nobel Prize in medicine for his discovery of tumor-inducing viruses. ...

Although Dr. Rous’s discovery was dismissed by the scientific community of his day as utter nonsense (everyone “knew” cancer

was not an infectious disease, so how could it be caused by a virus?), his work became in the last two decades a pillar of cancer research.

#### Announced Finding in 1911:

When Dr. Rous announced his “discovery” to the world in 1911 that a highly malignant chicken cancer called sarcoma could be transmitted to healthy chicks by injecting them with a cell-free extract of the tumor, he was careful to avoid the word “virus.”

At the time, scientists hardly knew what viruses were. Only a few viruses had been recognized, and these were known only by their action as disease-causing agents. It was not until the invention of the electron microscope some 20 years later that scientists could see a virus for the first time.

Dr. Rous’s discovery follows a visit by a New York City farmer to his laboratory at Rockefeller University. The farmer brought a Plymouth Rock hen that had a breast tumor. Dr. Rous, who diagnosed the tumor as a sarcoma, ground it up and mixed it with a salt solution into a “soup,” which he then passed through a series of ultrafine earthenware filters to remove all the whole cancer cells and bacteria.

#### Work Meet With Scorn:

When he injected the cell-free filtrate into healthy chicks from the same flock (which the farmer happily supplied), some of the chickens developed sarcomas.

The scientific community scoffed at the suggestion that the cell-free filtrate contained a virus which caused the cancer. Dr. Rous was accused of faulty technique and letting some cancer cells inadvertently slip through into the filtrate.

The work was further scorned when the Rous technique failed to reveal a specific virus associated with cancer in mammals.

... he remained unperturbed by the controversy surrounding his work ...

\* \* \*



George Papanicolaou (1883–1962) was a Greek physician and microscopist who immigrated to the United States in 1913 along with his wife and life-long assistant-to-be, Mary Papanicolaou. Given his skills, Papanicolaou soon found work in the Department of Pathology at New York Hospital which at the time was affiliated with Cornell Medical College. His first research project involved delineating and monitoring the estrous cycle of guinea pigs through the use of vaginal smears (obviously, obtained with very tiny speculums).

In the early 1920s, Papanicolaou began the longitudinal study of human vaginal smears using volunteers from the Cornell Medical College, including his wife, Mary, who provided daily smears for some twenty-one years. Upon examination of one particular smear from a participant's vaginal fluid, and to Papanicolaou's surprise, abnormal cancer cells were clearly visible. As he stated later, "the first observation of cancer cells in a smear of the uterine cervix was one of the most thrilling experiences of my scientific career." Papanicolaou's excitement was understandable given the obvious importance of an early screening method that could lead to further diagnostic testing, and possibly to an early effective treatment for this type of cancer. At the time, cervical cancer was the leading cancer killer among American women.

In 1928 Papanicolaou published a paper on his method for detecting early cervical cancer from vaginal smears in the Proceedings of the Third Race Betterment Conference held in Battle Creek Michigan. As an understatement, this was not a very receptive outlet. It wasn't until later in 1941 while working with Herbert Traut, another doctor and eventual coauthor at the Cornell Medical College, that

a more suitable manuscript appeared in the *American Journal of Obstetrics and Gynecology* entitled "The Diagnostic Value of Vaginal Smears in Carcinoma of the Uterus." The introduction and end summary of this paper are given below:

The death rate from carcinoma of the female genital tract is approximately 32,000 per year in the United States and of this figure, four-fifths, or 26,000 deaths per year, may be said to be due to cancer of the uterus. This rate has remained practically constant during the past twenty-five years.

One of the factors probably responsible for this rather discouraging situation is the fact that, despite the progress in methods of treatment, no significant improvement has been achieved in the diagnosis of malignant growths of the female genital tract, more particularly in their early stages. Indeed, it seems very likely that until enough is known about the etiology of cancer to make it possible to place efficient prophylactic weapons in physicians' hands, no radical change in the picture can be expected unless the introduction of new methods makes possible an early diagnosis of the disease.

Early diagnosis and treatment yield a high percentage of cures in both carcinoma of the fundus and of the cervix. The present difficulty in accomplishing an early diagnosis lies in the fact that we must depend largely upon the subjective symptoms of the disease to bring the patient to the physician, and by the time the patient becomes sufficiently aware of discomforts to seek help, the disease is far advanced. Even when the patient is seen early, the technique for making a positive diagnosis is not simple, as it involves a biopsy followed by the procedures necessary for microscopic examination, all of which are time consuming and relatively expensive. If by any chance a simple, inexpensive method of diagnosis could be evolved which could be applied to large numbers of women in the cancer-bearing period of life, we would be in a position to discover the disease in its incipiency much more frequently than is now possible.

It is our purpose to present in this preliminary report the results of experimentation with such a method of diagnosis which appears to have great possibilities and which has been in use at the New York Hospital for the past eighteen months.

One of us (Papanicolaou) has studied the normal and abnormal variations in the vaginal smear in women and in animals for many years. Through these studies, which have been conducted since 1923 at the Woman's Hospital, at the New York Hospital, and at the Memorial Hospital, he has become aware of the fact that carcinoma of the fundus and carcinoma of the cervix are to some extent exfoliative lesions, in the sense that cells at the free surface of the growth tend to be dislodged and subsequently find their way into the vagina. Furthermore, a technique for collecting the cellular debris, smearing it upon glass slides, and staining it has been perfected, so that the various components may be studied. The method is so simple and inexpensive that it may be applied to large numbers of women.

...

In presenting this method of diagnosis at this time, we hope that it may prove to be a dependable means whereby the principal malignant diseases of the uterus can be recognized; and further that because of its simplicity, it may eventually be applied widely so that the incipient phases of the disease may come more promptly within the range of our modern modes of treatment which have been proved highly effective in early carcinoma. In conclusion, it may be well to reiterate that whereas the method makes the material for examination easily and frequently obtainable at low cost, the interpretation of the smear requires the services of a careful and discriminating cytologist who has had experience in this field. Few persons can be depended upon for this work at the present time; however, if the method proves to be worthy of further development, as we expect it to be, then it will be possible in a relatively short time to provide the necessary facilities for instruction.

The development of the Pap smear to screen for uterine cancer in its early stages is a good example of abductive reasoning arising from some initial set of “surprising observations.” Here, Papanicolaou saw the unusual abnormal cells in a smear from someone diagnosed to have cervical cancer, which then led to the whole field of cytology (or maybe better, cytopathology) focused on the microscopic examination of cells as a screen for various diseases. Papanicolaou himself can be considered the “father of exfoliative cytology,” concerned generally with the shedding of tissue or cells and their ensuing microscopic examination.

The story of Papanicolaou’s discovery of a screening mechanism for cervical cancer that can be done early enough to allow treatment and prevent its fatal development is well-told by Erskine Carmichael in: *The Pap Smear: Life of George N. Papanicolaou* (1973, Charles C. Thomas, Springfield, Illinois). Even though the Pap test is not viewed as being a true diagnostic method, but rather is considered only a screening mechanism for determining which women need further assessment, it is still recognized by many as the Twentieth Century’s most significant advance in cancer control.

\* \* \*

Barach Blumberg (1925–2011) is the medical researcher who finally identified the hepatitis B virus, now known to cause epidemic yellow jaundice and, at times, to provoke liver cancer. In the early 1960s, Blumberg was studying blood samples from diverse categories of individuals to determine why certain ethnic groups might vary in disease susceptibility. A “surprising” reaction occurred when Blumberg mixed the blood serum from a New York hemophiliac with that

of an Australian aborigine. An antigen present in the aborigine blood reacted with an antibody present in the blood of the hemophiliac. The antigen was henceforth named the “Australian antigen,” and eventually turned out to be a surface antigen of the hepatitis B virus.

A number of sets of “surprising” circumstances and ensuing abductive conjectures finally led to the identification of the hepatitis B virus. This story is well-told by Blumberg’s co-researcher, Harvey Alter, in a 2011 issue of *Nature*. Part of this remembrance follows:<sup>1</sup>

... Blumberg had been using serum samples from hemophiliacs who had received multiple blood transfusions to provide antibodies that would react in agar with diverse proteins. The initially designated ‘red antigen’ was the result of an antibody in the serum of a hemophiliac from New York interacting with an antigen in the serum of an Australian Aborigine, and was later named the Australia antigen. Others might have dismissed this obscure finding as an irrelevant curio. But Blumberg’s hypothesis-generating mind was set in motion.

After finding that the antigen was 100 times more prevalent in patients with leukaemia than in healthy blood donors, Blumberg proposed that it was inherited and that it predisposed carriers to leukaemia. Although this speculation was later disproved, it led to critically important studies on patients with Down’s syndrome, who were known to have an inherited predisposition to leukaemia.

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<sup>1</sup>The story of how the hepatitis B virus was identified is reviewed in detail by Baruch Blumberg himself in: *Hepatitis B: The hunt for a killer virus* (2002; Princeton University Press, Princeton and Oxford). The summary citation for Blumberg’s 1976 Nobel Prize reads as follows: Jaundice stems from inflammation in the liver and is a symptom of different types of hepatitis. At the end of the 1960s Baruch Blumberg unexpectedly discovered an infectious agent for hepatitis B while researching blood proteins from people in different parts of the world. He demonstrated that the infectious agent was linked with a virus of a previously unknown type. The virus can be carried by people who do not become sick from it. These discoveries made possible both vaccines and tests to prevent spreading the disease through blood transfusions.

In 1964, shortly after Blumberg moved from the NIH to the Fox Chase Cancer Center in Philadelphia, Pennsylvania, he and his colleague Tom London discovered that although the Australia antigen was found at high prevalence in Down's patients as a group, it was not present in newborns. Rather than being inherited, the presence of the antigen in the blood of a Down's patient seemed to correlate with their living in a mental-health institution. This was the first clue that the Australia antigen might be related to an infectious agent. The specific infection was identified as hepatitis B when two Down's syndrome patients and an investigator in Blumberg's lab were found to carry the antigen only after developing acute hepatitis.

The US company Abbott Laboratories developed a test to screen blood donors for the antigen, which dramatically reduced the incidence of hepatitis B associated with blood transfusions. The test also identified pregnant women who carried the virus and led to measures that reduced mother-to-infant transmission by 90%.

In the late 1960s, Blumberg and Irving Millman, also at Fox Chase, postulated that the small, non-infectious Australia antigen particle could be separated from the virus and serve as a vaccine. A hepatitis B vaccine – initially produced from the plasma of infected individuals but now manufactured through genetic engineering – was developed by Maurice Hilleman at Merck and has prevented millions of hepatitis B infections. It was also the first cancer vaccine, as hepatitis B virus is a leading cause of liver cancer. For his discoveries, Blumberg received the Nobel Prize in Physiology or Medicine in 1976.

\* \* \*

The German virologist, Harald zur Hausen (1936–2023), received the 2003 Nobel Prize in Physiology or Medicine “for his discovery of human papilloma viruses causing cervical cancer.” The full Nobel Prize citation reads follows:

The growth, division, and death of living cells are regulated by their genes. If these functions are out of balance, tumors can form. One reason for this may be the incorporation of virus genes into the genes of host cells. Harald zur Hausen demonstrated in 1983 that cervical cancer in humans is caused by certain types of papilloma viruses (wart viruses), the genes from which are incorporated into the host cells' DNA. This discovery made it possible to develop a vaccine against cervical cancer, which had been the second most common tumor disease in women.

As might be expected, zur Hausen's research was guided by a series of "surprising" observations and attendant abductive conjectures. For example, going back to the nineteenth century, the anomalous situation existed that female prostitutes were much more likely to develop cervical cancer than were nuns, suggesting the hypothesis that cervical cancer was a sexually transmitted disease. A second "surprising" situation was encountered when the common conjecture was proven wrong that the herpes simplex virus caused cervical cancer. This disconfirmation resulted from the herpes virus DNA not being identifiable in cervical cancer samples.

As is now well-known, there are many types of human papilloma viruses (HPVs) with some causing warts, genital and otherwise. In the early 1970s, zur Hausen had reports that some genital warts could at times become cancerous. Based on these "surprising" observations and because warts are HPV driven, zur Hausen conjectured in 1976 that HPV played a role in the development of cervical cancer. But it wasn't until 1983 that zur Hausen was able to identify the presence of HPV-16 in cervical cancer tumors, and some time thereafter, the second major cause, HPV-18. In his Nobel Prize biography, zur

Hausen summarizes the path followed in the identification of HPV-16 and 18 as causative factors in cervical cancer:

... Cervical cancer had long been suspected of being caused by an infectious agent. In the late 1960s Herpes simplex type 2 (HSV-2) emerged as the prime suspect based on some seroepidemiological observations. Since our previous EBV [Epstein-Barr virus] work led to the identification of EBV DNA in specific human cancers, I had asked my colleague Heinrich Schulte-Holthausen to use the same technique to search for HSV-2 sequences in cervical cancer biopsies. All attempts, however, failed.

During the previous years I had studied a large number of anecdotal reports describing malignant conversion of genital warts into squamous cell carcinomas. Since genital warts had been shown to contain typical papilloma-virus particles, this triggered the suspicion that the genital wart virus might represent the causative agent for cervical cancer. Based on this hypothesis we initiated our papilloma virus programme in Erlangen. With the aid of the local Dermatology Hospital we received a large number of wart biopsies. Viral particles could be extracted from plantar warts and in 1974 we published our first report, demonstrating a cross-hybridization of the plantar wart virus DNA with some warts, but by far not with all of them. Genital warts and cervical cancer biopsies were negative. This was our first hint that there exist different types of papilloma viruses. In the following years our group ... [was] able to identify the plurality of the human papilloma virus family by isolating a steadily increasing number of novel types.

... Late in 1979 my co-workers Lutz Gissmann and Ethel-Michele de Villiers successfully isolated and cloned the first DNA from genital warts, HPV-6. It was initially disappointing not to detect this DNA in cervical cancer biopsies. HPV-6 DNA, however, turned out to be helpful in isolating another closely related genital wart papillomavirus, HPV-11, initially from a laryngeal papilloma. By using HPV-11 as a probe, one out of 24 cervical cancer biopsies



turned out to be positive. In addition, in other biopsies some faint bands became visible, permitting the speculation that they might represent hints of the presence of related, but different HPV types in these cancers. Two of my former students; Mathias Dürst and Michael Boshart, were asked to clone these bands. Both of them were successful. In 1983 we were able to document the isolation of HPV-16, in 1984 the isolation of HPV-18 DNA. We noted from the beginning that HPV-16 DNA was present in about 50% of cervical cancer biopsies, HPV-18 in our early experiments in slightly more than 20%, including several cervical cancer cell lines, among them the HeLa line.<sup>2</sup>

...

The early hypothesis that cervical cancer was caused by papilloma viruses, the successful isolation and characterization of the two most frequent HPV types in this cancer and the subsequent steps leading to a better understanding of the mechanism of HPV-mediated carcinogenesis and eventually to the development of a preventive vaccine were cited as the prime reasons for awarding one half of the Nobel Prize for Medicine or Physiology to me in 2008.

\* \* \*

To obtain a sense of what a current Artificial Intelligence (AI) model might provide in discussing abductive reasoning in the context of a real-life problem, ChatGPT was asked to “write about the contributions of Harald zur Hausen and how it reflects abductive reasoning.”

ChatGPT said:

Harald zur Hausen was a German virologist who made groundbreaking contributions to medical science by establishing the link between human papillomavirus (HPV) and cervical cancer. His

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<sup>2</sup>This refers to the infamous cell lines documented in the book by Rebecca Skloot, *The Immortal Life of Henrietta Lacks* (2010).

work was revolutionary because it challenged prevailing assumptions about the causes of cervical cancer and laid the foundation for life-saving vaccines.

### Contributions of Harald zur Hausen

#### Discovery of HPV's Role in Cervical Cancer

Before zur Hausen's research, the dominant hypothesis was that cervical cancer was caused by the herpes simplex virus (HSV). However, he hypothesized that certain types of HPV were responsible for cervical cancer instead. Despite skepticism from the scientific community, he pursued this hypothesis.

#### Identification of HPV-16 and HPV-18

In the early 1980s, zur Hausen and his colleagues identified HPV-16 and HPV-18 as the primary high-risk strains associated with cervical cancer. His findings provided direct evidence that these specific HPV strains were present in cervical cancer tissue, thus demonstrating a causal relationship.

#### Impact on Cancer Prevention

Zur Hausen's research paved the way for the development of HPV vaccines, such as Gardasil and Cervarix, which have significantly reduced the incidence of cervical cancer worldwide. His work also led to improved screening methods, such as HPV DNA testing, for early detection of cervical cancer risk.

#### Recognition and Nobel Prize

In recognition of his contributions, Harald zur Hausen was awarded the 2008 Nobel Prize in Physiology or Medicine. His research reshaped the understanding of virus-induced cancers and highlighted the importance of viral oncology in preventive medicine.

#### Reflection of Abductive Reasoning in His Work

Abductive reasoning is a form of logical inference in which the best or most plausible explanation is chosen based on limited evidence. It differs from deductive reasoning (which moves from gen-

eral premises to specific conclusions) and inductive reasoning (which generalizes from specific observations).

Zur Hausen's approach to cervical cancer research exemplifies abductive reasoning in several ways:

#### Forming a Hypothesis Against Prevailing Assumptions

Instead of accepting the dominant view that herpes simplex virus caused cervical cancer, zur Hausen inferred from certain patterns that HPV might be involved. He observed that HSV did not consistently appear in cervical cancer cases, leading him to seek a better explanation.

#### Searching for the Best Explanation

The presence of HPV DNA in cervical cancer cells provided a compelling alternative hypothesis. Although not initially confirmed, the idea that specific HPV types were causing the disease was the most plausible explanation based on the available evidence.

#### Testing and Refining the Hypothesis

Through molecular biology techniques, zur Hausen and his team identified HPV-16 and HPV-18.

## Chapter 19

# The Identification of Beriberi As a (Thiamine) Deficiency Disease (1901)

A vitamin is a substance that makes you ill if you don't eat it.

— Albert Szent-Györgyi

Beriberi is a disease of the peripheral nervous system caused by a deficiency in the amount of thiamine (vitamin B<sub>1</sub>) consumed in an individual's diet. Typically, beriberi manifests as a loss of feeling in the hands and feet, as well as by a general wasting of muscle and absence of movement in the legs. The word “beri” in the Sinhalese (Sir Lankan) language means “weakness,” and when doubled as in “beriberi,” it denotes “extreme weakness.”

In the last half of the nineteenth century and just as a diet of white rice had become common, beriberi developed a prominence throughout all of Southeast Asia. As is now known, the milling of brown rice to produce white rice also removes the thiamine present in the rice bran that is protective against beriberi. Although beriberi was a problem throughout Asia, and, for example, was considered a “national” disease in Japan and especially for its navy, it was to be the particular threat posed in the Dutch East Indies (the Spice

Islands) that led to the eventual unravelling of the cause of beriberi and how it might be remediated.

In the later part of the 1880s the Dutch government formed a Royal Commission on Beriberi to study the disease and its causes. On its return from the Dutch East Indies in 1887 the committee's report concluded that beriberi certainly had an infectious origin although the offending organism had not been identified. A member of this initial commission, Christiaan Eijkman (1858–1930), was left behind and put in charge of the Dutch military hospital in Jakarta (1888–1896) with a mandate to continue the search for the elusive microbe, or at least for the toxin that the organism produced.

The “surprising observations” that eventually led Eijkman to the crucial abductive conjecture that there was something protective against beriberi in brown rice and something facilitative in a diet of white rice was made in terms of an unlikely animal model. In observing the courtyard of the hospital for which he was in charge, Eijkman noticed that the chickens housed there had contracted an unusual progressive form of paralysis akin to beriberi in humans. Moreover, this widespread paralysis ended abruptly when a new cook was installed and the diet of the chickens was changed from purely white to brown rice.

Eijkman repeated several experiments involving white and brown rice diets for chickens with results always consistent with his original observations. In addition, he showed that feeding only the brown rice coatings by themselves cured the paralyzed chickens in a few hours. Eijkman also failed to transmit the “disease” from sick to healthy chickens, and eventually abandoned any further search for a

causative microbe. For a time, however, Eijkman continued to believe that white rice must contain some type of toxin and the brown rice coating held an antidote.

Because of ill-health, Eijkman returned to Holland in 1896, and was replaced by a younger colleague, Gerrit Grijns (1865–1944), who continued and greatly expanded on Eijkman’s original dietary studies but still involving chickens as an animal model. Grijns eventually concluded that chicken neuritis, and by analogy human beriberi, was due to the lack of a certain but still unknown dietary factor. In 1901, Grijns provided a landmark publication that was the first to definitely state a direct relationship between a dietary component and a disease. The quote given below translated from the Dutch is from a paper by Kenneth Carpenter entitled “The Nobel Prize and the discovery of vitamins”:<sup>1</sup>

... there occur in various natural foods, substances which cannot be absent without serious injury to the peripheral nervous system. ... These substances are easily disintegrated ... which shows that they are complex substances and cannot be replaced by simple chemical compounds.

As might be expected, there was a widespread skepticism about chicken neuritis being the equivalent of beriberi in humans. Therefore, before a connection could be definitively established, it was necessary to observe the effects of diet on human subjects. Two such studies will be noted here — one is purely observational and the second experimental, and which today would be viewed as ethically problematic and most likely would not get past an Institutional Review Board:

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<sup>1</sup>[www.nobelprize.org/prizes/themes/the-nobel-prize-and-the-discovery-of-vitamins/](http://www.nobelprize.org/prizes/themes/the-nobel-prize-and-the-discovery-of-vitamins/)

Before returning to Holland in 1896, Eijkman had contacted Adolphe Vorderman (1844–1902) who was then in charge of the health conditions for all of the hundred plus prisons in the Dutch East Indies. Eijkman convinced Vorderman to carry out a non-experimental observational study of the incidence of beriberi in the prisons in relation to the diet fed the inmates. Out of 100,000 prisoners fed unpolished rice, there were only nine cases of beriberi; on the other hand, there were four thousand cases in the 150,000 inmates fed on white rice.

#### RICE AND BERI-BERI:

#### PRELIMINARY REPORT ON AN EXPERIMENT CONDUCTED AT THE KUALA LUMPUR LUNATIC ASYLUM

BY WILLIAM FLETCHER, DISTRICT SURGEON, KUALA LUMPUR, FEDERATED MALAY STATES.

DURING the year 1905 an epidemic of beri-beri broke out in the Kuala Lumpur Lunatic Asylum. Commencing in February, it reached its height in July and August, declining somewhat towards the end of December. Out of 219 lunatics treated in the asylum during the year, 94 persons were affected, of whom 27 succumbed to the disease. The chief constituent of the rations supplied to the inmates of the asylum was uncured (Siamese) [white] rice, and in view of the fact ... that beri-beri occurs chiefly amongst communities with whom such rice is the staple article of diet it was decided, with the sanction of the Government, to place half the lunatics on cured (Indian) [brown] rice. The Government readily gave its consent and the experiment was commenced on Dec. 5th, 1905. The result up to Dec. 31st, 1906 (i.e., one year and 26 days) was that 34 out of 120 persons fed on uncured [white] rice suffered from beri-beri and 18 died, whilst among 123 patients dieted on cured [brown] rice there were no deaths from beri-beri and only two cases, both of whom were suffering from the disease on their admission to the asylum.

In 1912, Sir Frederick Gowland Hopkins (1861–1947) published a paper reporting on an extensive series of animal feeding experi-

ments that led him to suggest the importance of tiny quantities of as yet unidentified substances crucial for animal growth and survival. Hopkins called these hypothesized substances “accessory food factors,” later to be renamed “vitamins.” This work led to Hopkins being awarded the 1929 Nobel Prize in Physiology or Medicine jointly with Christiaan Eijkman.

In this chapter and the next four to follow, the discovery narratives are provided for five different vitamins: B<sub>1</sub> (thiamine), A, D, C, and B<sub>3</sub> (niacin). Also, because the lack of a particular vitamin in the human diet generally leads to a different deficiency disease, these are also discussed in order: beriberi (B<sub>1</sub>, thiamine), night blindness/eye lesions (xerophthalmia) (A), rickets (D), scurvy (C), pellagra (B<sub>3</sub>, niacin). For a general reference that summarizes the relevant information on each vitamin, see:

Lee R. McDowell (2013). *Vitamin History, The Early Years*. (First Edition Design Publishing, Sarasota, Florida).

Each chapter will also generally include more comprehensive references that are specific to that particular vitamin and deficiency disease combination. So, for example, in this first chapter on beriberi, a complete presentation is available in:

Kenneth J. Carpenter (2000). *Beriberi, White Rice, and Vitamin B: A Disease, a Cause, and a Cure*. (University of California Press, Berkeley).



## Chapter 20

# Vitamin A As an Accessory Food Factor (1913)

A drug is a substance which, if injected into a rabbit, produces a paper.

— Otto Loewi (1873–1961)

The eventual identification of vitamin A was based on general nutritional studies in contrast to concentrating on curing or preventing a specific disease as was done for beriberi, rickets, scurvy, and pellagra. Although a vitamin A deficiency can lead to several vision difficulties such as night blindness (the inability to see well at night), and xerophthalmia (the formation of eye lesions), it was initially identifiable as just something that was necessary for normal growth in animals. The inference structure for these experimental nutritional trials was fairly simple: first, some set of “surprising observations” was seen as a result of the particular diets being imposed. The resulting abductive conjecture was then one of a missing component in the diets being used that would account for these “surprising observations.” A further manipulation may then add something more to the diet such as milk or butter. If the “surprising observations” no longer occur, it is assumed that some component in the added dietary

substance must be responsible. At this point attempts are made to isolate the specific accessory food factor(s), and then to characterize them chemically with a goal of eventual synthesis.<sup>1</sup>

As an early example of the experimental nutritional paradigm just described, Nicolai Lunin (1853–1937) for his doctoral research in 1881 at the University of Dorpat in Estonia showed that adult mice could develop normally and had healthy lives when raised on milk; however, mice could not survive when raised only on the separate milk components. As Lunin concluded:

Mice can live quite well under these conditions when receiving suitable foods (e.g., milk); however, as the above experiments demonstrate that they are unable to live on proteins, fats, carbohydrates, salts, and water, it follows that other substances indispensable for nutrition must be present in milk besides caseinogens, fat, lactose, and salts.

A number of other feeding experiments similar to that of Lunin were performed in the late Nineteenth and early Twentieth Centuries. One briefly mentioned in another chapter was carried out by the future Nobel Laureate Frederick Hopkins in 1912. Hopkins noted that young rats did not grow well when fed just a basic diet of starch, sugar, lard, protein, and minerals. But when a small amount of milk

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<sup>1</sup>Although the emphasis here will be on general issues of growth and the presence/absence of vitamin A, there were a few early connections between diets that are now known to be deficient in vitamin A and problems of vision. In particular, the work of Francois Magendie (1783–1855) might be noted as a relevant example. From 1816 and later, Magendie was interested in the nutritional value of nitrogen (i.e., protein) in foods. When dogs were fed only sugar (having no nitrogen) and distilled water, they grew thin and developed corneal ulcers, which eventually perforated; the dogs died shortly thereafter. A Parisian pediatrician colleague of Magendie, Charles-Michel Billard (1800–1832) noted that similar corneal ulcers were frequently present in abandoned infants in Paris and raised the possibility that eye ulceration could be linked to faulty nutrition.

was added, the rats reverted to normal growth. Hopkins comments that these unknown “accessory food factors” present in milk encouraged growth and supported life, and were found in “astonishingly small amounts.”

At the University of Wisconsin during the early 1910s, Elmer McCollum (1879–1967) and his unpaid assistant Marguerite Davis (1887–1967) reported that all fats were not equal when considering growth in rats. Rats grew normally on a diet of casein, lard, lactose, starch, and salts when an ether extract from butter or egg yolk was added. This fat-soluble substance was eventually identified and called vitamin A in 1920. Using a similar ether extract of lard or olive oil led to the animals dying. From this point on, McCollum repeatedly contended that he alone discovered vitamin A, contrary to several other similar nutritional experiments reported in the exact same year of 1913 as well as before. Irrespective of actual discovery priority, McCollum and Davis have been generally credited with the identification of the first accessory food substance to be recognized as a vitamin, called fat-soluble A by McCollum and Davis.

In 1917, McCollum moved from Wisconsin to John Hopkins University, taking all of the research notebooks with him from the whole Wisconsin laboratory, including those of a junior colleague, Henry Steenbock (1886–1967), who had worked in the laboratory since 1915.<sup>2</sup> McCollum subsequently published a 1918 paper in the *Journal of Biological Chemistry* that adopted Steenbock’s wording and experimental results in their entirety without giving him credit. The Chairman of the Department of Agricultural Chemistry, E. B. Hunt,

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<sup>2</sup>Henry Steenbock will reappear in the chapter on vitamin D.

felt compelled to offer a statement about the situation in *Science* (1918, 47, 220-221); this is reproduced below:<sup>3</sup>

#### PROFESSIONAL COURTESY

In the January, 1918, number of the *Journal of Biological Chemistry* appeared an article by E. V. McCollum and N. Simmonds, now of Johns Hopkins University, entitled “A Study of the Dietary Essential, Water-Soluble B, in Relation to Its Solubility and Stability Towards Reagents.”

This work, as the article indicates, was done, but not prepared for publication, in the laboratory of agricultural chemistry of the University of Wisconsin. The authorship of this article does not properly give credit to those participating in this research. On page 62 a footnote briefly states that “Credit is due Mr. H. Steenbock for the preparation of the extracts employed in this work.” This representation is a gross injustice to Professor Steenbock and displays a marked transgression of common professional courtesy and ethical standards on the part of the authors of this article. Professor Steenbock not only contributed much, if not all, to the thought expressed in the preamble of this article, but the details of making the vitamin preparations and the chemical work in reference to their stability reappear in the text practically verbatim as they were developed by him in his own notebooks. The method of experimentation on vitamin stability as published in this paper was the outgrowth of methods previously employed by Professor Steenbock in experiments with pigeons. He should at least have appeared as a joint author of this article.

Inasmuch as the records of rat feeding, although they were part of a continuing project of the experiment station, were removed in toto from the campus with the change in staff and consequently no longer available, it had not been possible for Professor Steenbock to correlate this material for publication.

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<sup>3</sup>The complete story of vitamin A discovery and *sequela* is told in detail by R. D. Semba (2012), *The Vitamin A Story: Lifting the Shadow of Death* (Karger, Basel, Switzerland).

E. B. HART

Chairman of the Department of Agricultural Chemistry, University of Wisconsin

Irrespective of any dubious overstatements of scientific contribution, McCollum did go on after Wisconsin to produce several clever and significant advances in the study of nutrition and vitamins. One such study will be mentioned here in closing this chapter on vitamin A. Soon after vitamin A was discovered, it was generally thought that rickets might also result from a vitamin A deficiency. In 1922, McCollum and associates provided experimental evidence that rickets was not due to a vitamin A deficiency. They first passed oxygen through cod liver oil until all vitamin A was destroyed. This later fact was demonstrated by an inability to cure xerophthalmia with the treated oil. The oxidized oil, however, was still effective against rickets implicating a vitamin in cod liver oil as its cure other than the destroyed A (and which we now know to be vitamin D).

## Chapter 21

# The Etiology of Childhood Rickets and Vitamin D (1918)

The shrewd guess, the fertile hypothesis, the courageous leap to a tentative conclusion – these are the most valuable coin of the thinker at work.

— Jerome Brunner (1915–2016)

Rickets is a condition typically seen in childhood that manifests through soft bones and decreased bone density, often resulting in bowed legs, curved spines, stunted growth, and other skeletal anomalies. The exact cause of rickets had been elusive until the 1920s when it was shown experimentally that the (rachitic) condition resulted from a vitamin D deficiency during the time a child's bones were being formed. Moreover, such a lack of vitamin D could result from two possible reasons: a dietary absence of vitamin D, such as that which might occur in exclusively breast-fed babies; or, because vitamin D can be photosynthesized through the exposure of skin to ultraviolet radiation, rickets could result from a child's lack of exposure to sunshine.

Rickets has been around for a long time, and documentation for it as a widespread condition exists from at least the time of the

Roman Empire. It became highly prominent in northern Europe from the eighteenth century onward, partially as a result of the industrial revolution where coal-fueled furnaces emitted enough gases to produce a smog that effectively eliminated sunlight as a possible source of vitamin D through photosynthesis. In fact, rickets became commonly known as the “English Disease,” even though it was well-documented in England before the industrial revolution and was widespread throughout all of northern Europe. For example, Francis Glisson (1597–1677) published an extensive treatise on rickets in 1650 (*De Rachitide*) that was translated from the original Latin into English as early as 1651. The disease of rickets itself had been included in the mortality tables of England since 1634.

In elucidating the paths followed in identifying a vitamin D deficiency as the cause of rickets, there are two major sets of “surprising” observations that eventually led to the two separate abductive conjectures of either a nutritional cause for rickets or a second possibility that was geographical and involved differential sunshine exposure. The overall abductive hypothesis, tested experimentally in the 1920s, of a vitamin D deficiency as the cause of rickets can be stated as follows: there is some unknown factor (later to be identified explicitly as vitamin D) either available in a diet or that can be manufactured by one’s own body when sunshine is present, which can prevent rickets. Or conversely, when ultraviolet radiation is not present and the unknown factor is not available in a diet, childhood rickets can develop.

Theobald Palm (1848–1928) graduated with a medical degree from Edinburgh University in 1874, and immediately joined the Edinburgh

Medical Missionary Society as a representative to the treaty port of Niigata in Japan. Coming from Scotland where the English Disease was rampant, Palm was struck by the complete absence of rickets over his whole ten-year term in the city of Niigata as well as in all other areas of Japan that he visited. Intrigued by this “surprising” absence of rickets, Palm contacted his contemporary medical missionaries throughout Asia and North Africa and asked about the climatic conditions and the prevalence of rickets for the regions in which they served. Upon his return to the UK, Palm made a similar assessment from available published sources of the geographical distribution of rickets presence and climate variation, particularly that of sunshine, throughout all of Europe and the UK. Palm’s conclusions about the relationship of rickets and sunshine were published in the *Practitioner* in 1890 under the title of “The Geographical Distribution and Etiology of Rickets.” Several summarizing excerpts follow:

With a view to eliciting information first hand from medical men practising among the native populations in China, India, and elsewhere, the writer has addressed a series of questions to medical missionaries in these countries with regard to the prevalence or absence of rickets, the habits of the people, and their climatic and sanitary conditions. Their testimony is valuable even where it is negative as to the occurrence of rickets. For, if we find the disease to be unknown where the diet and sanitary surroundings are even worse than in places where the disease prevails, we can no longer regard them as prime factors in producing the disease. On the other hand, if we can point out any condition common to those climates or localities where the disease is unknown, which is at the same time markedly deficient where the disease prevails, we may infer it to be the most important element in the case. The reader is asked to review the facts as to the distribution of the disease in the light of the theory that *sunlight* is essential to the healthy nu-



trition of growing animals, and that a deficiency of it characterises the localities or conditions of those who suffer from rickets, and is the most important element in the aetiology of the disease [*italics in the original*].

...

Now the most salient fact with regard to the climate of those counties which enjoy immunity from rickets is the abundant sunshine and clear sky. On the other hand, the feature of our British climate, which is most striking to any one who has lived for some years in the East, is the want of sunshine, and the dull gray skies, or frequent fogs. It is this which is most intensified in our towns, which are under a perennial pall of smoke, and where the high houses cut off from narrow streets a large proportion of the rays which struggle through the gloom. It is in the narrow alleys, the haunts and playgrounds of the children of the poor, that this exclusion of sunlight is at its worst, and it is there that the victims of rickets are to be found in abundance. Another reason why the poor suffer more than the rich, is because they cannot afford to send their children out in the air and sunshine. The mothers are taken up with household work, and themselves suffer from the same cause.

During the first several decades of the twentieth century, a number of (quasi-)experimental studies were performed that clearly identified ultraviolet (UV) radiation as a means for both curing and preventing rickets. We limit ourselves to a short summary of one such study done at the close of the first World War during the winter of 1918/1919 by the Berlin doctor, Kurt Huldshinsky, working at the Oskar-Helene-Heim children's hospital which cared for many children suffering from rickets. Noting the "surprising" observation that all his young rachitic patients were extremely pale, Huldshinsky conjectured that heliotherapy using quartz-mercury lamps might be of some help in alleviating the many overt manifestations of rickets.

Four children chosen to be experimental subjects were given two months of UV light exposure; three control subjects received no such therapy.

Based on objective X-rays of the lower left arm at the onset of the study and again at four and eight weeks, the experiment could be considered a complete success. More subjectively, Huldschinsky is quoted as writing (in an English translation of his seminal 1919 German article):

After two months of irradiation treatment, miserable, weak and fragile children had become strong and spirited, and they were all able to sit up without aid. Those who had previously just laid there passively on the cushions, could now bend their head backwards and upwards when lying on their stomach. Their breathing difficulties and cyanosis [a bluish color in the skin and lips caused by a shortage of blood oxygen] had disappeared, and they no longer succumbed to infections.

Many successful replications of the Huldschinsky heliotherapy experiments followed including studies where the radiation of just one arm led to a cure for rickets in both arms as documented by diagnostic X-rays. The evidence provided by Huldschinsky and others led to the widespread adoption of light therapy as an economical method for curing and preventing childhood rickets throughout all of Germany and Europe.

It is now well-known that cod liver oil is a potent source of the two vitamins, A and D. Considered a useful general medicinal from the Viking period in the eighth century onward, cod liver oil became known throughout Northern Europe as a specific curative for rickets from at least the end of the eighteenth century. As an example,

several excerpts are provided below from the English translation of *Lectures on Clinical Medicine Delivered at the Hôtel Dieu* written in 1861 by Armand Trousseau (1801–1867). Trousseau confidently stated that rickets is the result of a faulty diet but it can be cured through cod liver oil:

The manner in which M. Bretonneau, of Tours, was induced to give the [cod liver] oil in this disease deserves notice. He had treated the rachitic child of a rich Dutch merchant with preparations of iodine and other means, for some time, without success. He was then told by the father that the elder children had previously suffered under the same malady, and had been cured by the cod liver oil, which, in Holland, was a popular remedy. Bretonneau gave the same substance to his young patient, and was much struck with the very rapid and successful result which followed. He commenced making researches with it on other patients, and it was only then that he learnt for the first time what had been written by the German authors on this subject. He has since given it extensively in rachitis, with the happiest results.

...

Gentlemen, I am also strongly led to believe, that rickets and osteomalacia [ a softening of the bones] are the same disease, by the fact, that both are wonderfully combated by the same medication. This medication may be considered as really heroic in the treatment of rickets: it consists in giving cod-liver oil, and, in a more general way, fish oil.

The knowledge that cod liver oil was a curative for rickets leads to a secondary narrative for the actual discovery of vitamin D. Edward Mellanby (1884–1955) was a biochemist working at King's College for Women in London from 1913 to 1920 when he was asked to study the cause of rickets. In his investigation, Mellanby found that feeding confined dogs a diet only of porridge caused rickets that could

be cured through cod liver oil. He concluded that rickets was caused by the lack of a particular vitamin that could be found in cod liver oil. Elmer McCollum, the putative discoverer of vitamin A from the last chapter, decided to evaluate whether it was actually vitamin A that was the curative for rickets. He bubbled oxygen through cod liver oil destroying vitamin A as shown by the inability of the modified oil to prevent xerophthalmia. The modified oil, however, was “surprisingly” able to still cure rickets. McCollum (abductively) conjectured that cod liver oil had a second vitamin present apart from vitamin A, and this new vitamin was able to cure rickets – it was given the letter D.

Much of the work involving vitamin D from the 1920s onward was directed toward the chemically mundane task of identifying and isolating this particular accessory food factor. However, there is one more tale of abductive reasoning that can be presented, pertaining to vitamin D being produced merely by irradiating various foodstuffs. Harry Steenbock (1886–1967), working at the University of Wisconsin in the 1920s, was studying the effects of UV radiation in curing rachitic rats, and noticed a “surprising” set of observations: by merely occupying a previously irradiated rat’s cage, a new rachitic rat could also be cured. Steenbock abductively hypothesized that it might be the irradiated material left behind in the cage, such as excreta or millet used as food, which might be effecting a cure when eaten by a newly resident rat. Steenbock then explicitly radiated just the foodstuff (hog millet) used for a new rachitic rat and found that, as we now know, vitamin D is produced within the foodstuff and can effect a cure for a newly resident rachitic rat.

A short summary of Steenbock's discovery is given below as taken from a biographical sketch appearing in *The Journal of Nutrition* in 1973, written by Howard Schneider:

... Steenbock took advantage of Huldschinsky's demonstration in 1919, that ultraviolet light could be used to cure a rachitic animal. Previously, only cod-liver oil was a recognized agent capable of preventing or curing the faulty calcification of bone as observed in rickets ... In using ultraviolet light as an antirachitic agent ... Steenbock stumbled into a world of phenomenology from which he emerged with international fame. Fortune had favored the prepared mind.

The fundamental, puzzling phenomenon that Harry Steenbock unraveled, which confronted him repeatedly in different ways and was exhibited in a variety of circumstances, was that the beneficial effects of ultraviolet irradiation of an experimental animal could be transferred by that irradiated recipient to another unirradiated animal by the mere act of their occupying a common space, either simultaneously or, even more puzzling, in series, provided the irradiated animal preceded the unirradiated. Much of this became explicable ultimately by the recognition that excrement and perhaps other effluvium, such as salivation, could convey the infinitesimal amounts of physiologically active material from the irradiated to the unirradiated recipient, not unlike fomites conveying infection. But it was in the struggle toward this understanding that Steenbock instructed his assistant ... to irradiate the hog's millet ... [and] food, the very substance of nutrition, became the storehouse of the antirachitic effects of ultraviolet light. A food previously lacking in the antirachitic vitamin, by its irradiation with ultraviolet light now had the vitamin activity. Harry Steenbock, as a popular writer of the day put it, had trapped the sun.

The process of irradiation by UV light to increase the vitamin D content in food and other organic matter was patented by Steen-

bock soon after his discovery. This specific patent led to the first university technology transfer office, the Wisconsin Alumni Research Foundation (WARF). In 1927, WARF completed its first licensing agreement with the Quaker Oats company which then fortified their cereals with vitamin D. WARF went on to license the technology to several pharmaceutical companies for medical applications. The majority of the money WARF receives through the various patents developed from Wisconsin faculty still goes back into the research enterprises of the University (for instance, see the discussion elsewhere of the anticoagulant warfarin).

## Chapter 22

# The Identification of Scurvy As a (Vitamin C) Deficiency Disease (1928)

If we exclude straightforward famine, scurvy is probably the nutritional deficiency disease that has caused the most suffering in recorded history.

— Kenneth J. Carpenter (*The History of Scurvy & Vitamin C*) (1986)

Scurvy is a disease of deficiency caused by the lack of vitamin C (ascorbic acid) in a person's diet. It is also one of the oldest and most dreadful diseases known to mankind. Disease symptoms include general fatigue and weakness, swelling of the limbs, gum disease with loss of teeth, bleeding from the skin, poor wound healing, and related bodily degenerations that can ultimately lead to death. Although most animals are able to manufacture their own vitamin C, humans and several other animals such as the guinea pig, cannot. It typically takes at least a month of little to no vitamin C for the scurvy symptoms to appear. Historically, scurvy was mainly associated with malnutrition, but it became a particularly severe problem during the Age of Sail, roughly the three-hundred-year span from around 1570 to 1870 when large sailing ships were relied on for trade, travel, and war. During this period, it was generally assumed that half of all sailors would die of scurvy on any major voyage. It is estimated that

two million sailor deaths from scurvy, commonly referred to as the “plague of the sea,” occurred during the Age of Sail.

Throughout the Age of Sail it was periodically recognized but also recurrently forgotten that ship crews showing the symptoms of scurvy after an extended voyage could be cured if supplied with fresh fruits and vegetables when an appropriate port was reached. The Spanish knew of the efficacy of citrus fruits as a remedy for scurvy from at least the last half of the Sixteenth Century. But it would not be until 1795 that English health reformers with the Royal Navy such as Gilbert Blane (1749–1834) persuaded the Royal Navy to routinely provide lemon juice to its sailors on long voyages. The later replacement of lemon juice by the somewhat inferior lime juice is the origin of the nickname “limey” for a British sailor. This belated recognition of the connection between scurvy and the lack of citrus fruit is even more surprising given that a Scottish surgeon in the Royal Navy, James Lind (1715–1794), had shown in 1747 in what is now famously considered one of the first ever clinical trials that citrus fruits could alleviate scurvy. In hindsight, it is a rather remarkable failure of the British Royal Navy to not to have seized on all these “surprising observations” before they did, and formulate a general (abductive) conjecture that there must be something present in fresh fruits and vegetables, particularly citrus, that is both curative and preventive of scurvy.

Axel Holst (1860–1931) was a Norwegian Professor of Hygiene and Bacteriology at the University of Oslo, who together with his pediatrician colleague, Theodor Frølich (1870–1947), began a study of a scurvy-like condition called “shipboard beriberi” that severely af-



affected the Norwegian fishing fleet. Suspecting a nutritional deficiency as a cause for the condition, Holst and Frølich chose two possible animal models to assess the condition – the pigeon, which was a common vehicle for the study of beriberi, and the familiar guinea pig. The choice of the guinea pig was truly fortunate since humans and guinea pigs are among the few animals that cannot produce their own vitamin C, and therefore can develop scurvy.

Relying on the animal model of the guinea pig, Holst and Frølich carried out a systematic evaluation of factors that could produce the ship-related dietary deficiency disease, and of those substances having a preventive or curative value. So, for example, a diet consisting solely of various types of grain produced scurvy-like symptoms in the guinea pig, but these manifestations were absent when a diet was supplemented with known antiscorbutics such as lemon juice or fresh cabbage. Pigeons never did develop such symptoms, because as we now know, they could produce their own source of vitamin C.

Although the Holst/Frølich findings were published in 1907, they were not well-received initially mainly because the notion of a nutritional deficiency was rather unfamiliar at the time. It was the work of Casimir Funk (1884-1967) working at the Lister Institute in London that proposed in 1912 the existence of at least four substances (vitamins) that could prevent the various deficiency diseases of beriberi (“antiberiberi” or vitamin  $B_1$  (thiamine)), scurvy (“antiscorbutic” or vitamin C), pellagra (“antipellagic” or vitamin  $B_3$  (niacin)), and rickets (“antirachitic” or vitamin D). It might also be recalled from the discussion of beriberi in a previous chapter, 1912 was the same year that Frederick Gowland Hopkins (1861–1947) hypothesized the

existence of what he labeled “accessory food factors” that were necessary for animal growth and survival. Although all the various “surprising observations” based on experimentation with diet led to the abductive conjecture of “vitamins” and “accessory food factors,” it would still be some time before these substances could be isolated, and even longer to when they could be synthesized.<sup>1</sup>

The isolation of vitamin C was first achieved by a Hungarian scientist, Albert Szent-Györgyi (1893–1986), although it would take some time before this particular fact would be recognized. Working for a period in the Cambridge laboratory of Frederick Hopkins in 1928, Szent-Györgyi had been intrigued by the similarity between the darkened skin and gums of patients with Addison’s disease and the discoloring or oxidation of cut apples, potatoes, and plants generally. Szent-Györgyi conjectured that “normal” patients would have an antioxidant present in their adrenal glands, situated just above the kidneys in most animals, that would prevent color change in the skin but which would be absent in those with Addison’s disease.<sup>2</sup> In the collection of adrenals glands Szent-Györgyi obtained from the local slaughterhouses, he observed a “surprisingly” high concentration of a “reducing” chemical (i.e., a hydrogen-donating antioxidant) in the adrenal cortexes. He determined its chemical structure to be  $C_6H_8O_6$ . Several common sugars such as glucose and fructose have a

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<sup>1</sup>One somewhat counterintuitive historical aspect of scurvy is its occurrence in the later Nineteenth Century in an infantile form among children who were born into upper-class families. Many of these privileged children were not breast-fed and instead were on a cow’s milk diet that had been pasteurized. The heat used for this process destroyed the vitamin C present in the milk and made such children vulnerable to a vitamin C deficiency if their diets were not supplemented in other ways.

<sup>2</sup>This conjecture is reflective of Szent-Györgyi’s lifelong credo: to see what everyone else has seen, but think what no one else has thought.

similar chemical structure with the  $H_8$  being replaced by  $H_{12}$ . These were known as “hexoses” for the six carbon atoms ( $C_6$ ), and with the “ose” referring to the substances being sugars.

In submitting his work to a journal, Szent-Györgyi had named the identified substance “ignose,” where “ose” stood for “sugar” and “ig” from the Latin “Ignosco” for “I don’t know.” The editor objected to the flippant name so upon resubmission, Szent-Györgyi substituted “godnose.” The editor promptly renamed it “hexuronic acid” for its six carbon atoms. It is of interest to note that Szent-Györgyi was also able to obtain this hexuronic acid from orange juice and extracts of cabbage, a propitious circumstance for the later identification of hexuronic acid as the elusive vitamin C.

During part of the period from 1928 to 1932, Szent-Györgyi spent time at the Mayo Clinic in Rochester, Minnesota, where adrenal glands could be supplied in abundance from the stockyards located nearby in St. Paul. Although this stockpile of hexuronic acid was large, it was almost exhausted when Szent-Györgyi returned to Hungary in 1932 to take up a Professorship at the University of Szeged. It was here that his dislike for the Hungarian red peppers his wife tried to serve him led Szent-Györgyi to a rich source of hexuronic acid that could be produced locally in bulk.

In 1932, Glen King and colleagues at the University of Pittsburgh were attempting to isolate vitamin C from lemon juice. In a paper published in *Science* (April 1, 1932), entitled “The Chemical Nature of Vitamin C,” the Pittsburgh group reported on the process of extracting vitamin C crystals from lemon juice, and commented that it had all the properties of the hexuronic acid of Szent-Györgyi,

and most significantly, it was protective against scurvy in guinea pigs. Two weeks later, Szent-Györgyi and a researcher from King's laboratory in Pittsburg, Joseph Svirbely, published a note in *Nature* entitled "Hexuronic Acid as the Antiscorbutic Factor," which reported on a similar trial that again used guinea pigs. Irrespective of what group might eventually receive priority, it was Szent-Györgyi who was awarded the 1937 Nobel Prize for Physiology or Medicine "in recognition of his discovery concerning the biological oxidation processes with special reference to vitamin C ... "

There are two sources that the reader might consult for further details about scurvy and the discovery of vitamin C:

Kenneth J. Carpenter (1986). *The History of Scurvy & Vitamin C*. Cambridge University Press, Cambridge, England.

Ralph W. Moss (1988). *Free Radical: Albert Szent-Györgyi and the Battle Over Vitamin C*. Paragon House Publishers, New York.

## Chapter 23

# Pellagra and Niacin (Vitamin B<sub>3</sub>) Deficiency (1937)

To all my little Hulkamaniacs, say your prayers, take your vitamins, and you will never go wrong.

— Hulk Hogan (1953– )

The word “pellagra” is Italian for “rough skin,” and refers to a dietary deficiency disease now known to be caused by the lack of niacin (vitamin B<sub>3</sub>) in an individual’s diet. As typically introduced, pellagra is characterized by a variety of skin rashes plus an increasingly dire set of four “Ds”: diarrhea, dermatitis, dementia, and death. At one time in the late Nineteenth and early Twentieth Centuries, pellagra was particularly prevalent among the rural poor both in the Southern United States as well as in the countries around the Mediterranean where locally-grown corn provided the bulk of one’s daily diet. This “surprising” observation or connection led to an incorrect abductive hypothesis that corn harbored an infectious agent that could be passed along from one individual to the next, possibly by an insect vector similar to the mechanism for yellow-fever and malaria transmission. Another incorrect explanation for pellagra was the “spoiled (or moldy) corn” conjecture that was akin to ergotism,

the toxic condition caused by ingesting food contaminated with the ergot fungus.

Maize, more commonly known as corn in North American English, was domesticated some 9,000 years ago from wild teosinte by the indigenous people of southern Mexico. Its cultivation spread soon thereafter throughout all of the Americas. Maize was transported to the European continent after the New World arrival of Christopher Columbus in 1492. By the Seventeenth Century it was the common peasant food throughout much of Southern Europe as well as in North America. At present, maize is still cultivated globally, and as a crop has the greatest total weight compared to any other grain.

Although maize may have become a widely cultivated grain outside of the immediate Mesoamerican region where it was first domesticated, a procedure for the further processing of maize as a food stuff, called nixtamalization, was unfortunately not passed along. Nixtamalization is a procedure for preparing maize for further use where the grain is soaked and cooked in an alkaline solution until it can be hulled and washed. The alkaline solution is commonly made using calcium hydroxide, called “cal” in Spanish. This nixtamalization process transforms the dry maize kernels into a soft and fragrant masa or corn dough that can be used easily for tortillas, tamales, and other similar food entities. But even more importantly, nixtamalization makes two substances present in corn bioavailable – niacin (vitamin B<sub>3</sub>), and the essential amino acid of tryptophan that can be transformed into niacin by the human body. In addition, tryptophan is the basis for making melatonin and serotonin which help regulate pain, sleep, and mood.

When maize was cultivated globally and eaten as the primary staple without undergoing a process of nixtamalization, pellagra became common. The first clear descriptions of the dermatological manifestations of what is a niacin deficiency disease were made in Spain in 1735 by the physician Gaspar Casal (1681–1759). Casal described a distinctive red rash that appeared on the neck, soon to be known as “Casal’s collar” or “necklace.” Similar characteristic red rashes present on the hands and feet were referred to as *mal de la rose* by Casal. His major medical work, *Natural and Medical History of the Principality of Asturias*, was published posthumously in 1762. This led to the niacin deficiency disease being referred to as “Asterian leprosy” – it is now recognized as the first modern pathological description of a syndrome, where here the syndrome is one of pellagra.

In the early 1900s pellagra reached epidemic proportions in the American South, particularly among the rural poor with their cornmeal based diets. So, for example, between 1906 and 1940 some three million Americans were affected by pellagra, leading to more than 100,000 deaths. In 1914, the U.S. Surgeon General assigned the physician and epidemiologist from the U.S. Public Health Service, Joseph Goldberger (1874–1929), to study pellagra and hopefully find a cure. Goldberger first showed that pellagra was linked to diet by studying its occurrence in various residential institutions such as orphanages, mental hospitals, and prisons. He noted, for example, the “surprising” observation that children in the age ranges where milk was *not* being routinely provided, tended to have pellagra. Goldberger also conjectured (abductively) the noninfectious nature of pellagra by noting the unusual circumstance that doctors,

nurses, and other attendants in close contact with pellagra patients did not themselves acquire it. Because the institutional staff typically had the first choice among the foods prepared within the institution, and also ate at least some of their meals outside of the institutional setting, they did not rely solely on the same type of restricted diet that tended to produce a deficiency disease.

Goldberger conducted two parallel experiments starting in 1914. In one of these, two orphanages were selected having serious cases of pellagra (172 positive pellagra cases and 168 that were negative). With federal funding, Goldberger switched to a more varied diet for the orphanages that included fresh meat, milk, vegetables, and eggs. After several weeks, no new cases of pellagra occurred, and almost all of the previously afflicted orphans had recovered. There was only one new case of pellagra over the two years that the study ran. Unfortunately, once the federal funding was removed and diets reverted to what they had been before the intervention, the prevalence of pellagra returned to the same levels it had been before the change. So, inadvertently, the reversion to the original diet again demonstrated the basic dietary cause of pellagra.

The second experiment took place at the Georgia State Sanitarium and involved a control group that received the same diet they had before, and a second experimental group with a more varied and balanced diet. After two years, half of the control group was sick with pellagra but everyone in the experimental group was well. In a smaller study, Goldberger was also able to induce pellagra experimentally in six subjects through a restrictive diet given to eleven total prisoners who received their freedom after participation in the study



(and who, presumably, could have better diets thereafter). Also in 1916, Goldberger conducted several “filth parties” with a number of volunteers including himself, his wife, and assistant. In one such party, injection of pellagic blood was carried out over a number of trials. Although diarrhea and nausea were experienced, pellagra was not. Similarly, other ingestions from pellagra patients such as fecal matter and skin scrapings in capsule form did not induce the deficiency disease.

Several researchers at Yale in 1916, Russell Chittenden and Frank Underhill, showed that the type of diet leading to pellagra in humans would produce a “black tongue” condition in dogs. In this way an important experimental animal was identified that could be used in further controlled studies of pellagra production. The type of diet leading to pellagra in humans and “black tongue” in dogs was generally referred to as the “three M diet” – meat (or “fatback” from the pig), molasses, and meal (corn). As its name suggests “fatback” is taken from the back of a pig, and consists primarily of subcutaneous fat located just under the skin. It contains a high proportion of fat relative to lean meat, and contained little niacin or the precursor amino acid of tryptophan.

Starting in 1922 and continuing until his death in 1929, Goldberger experimented with the canine black tongue through the feeding of the same corn-based diet as he had given to prisoners. In this way, he demonstrated that the P-P (pellagra-preventive) factor was present in lean meat and milk, and also in the much cheaper dried brewer’s yeast. Goldberger and colleagues showed that a heat-stable yeast component prevented the occurrence of black tongue. On the basis

of all his animal experimentation, Goldberger concluded in 1926 that the P-P factor was the heat-resistant part of “water soluble vitamin B.” After 1928, yeast was given free to areas of endemic pellagra by state and county health departments and the American Red Cross.

Right before he died, Goldberger and colleagues showed that a liver extract could prevent black tongue. Later, in 1937 a nutritional biochemist at the University of Wisconsin, Conrad Elvehjem (1901–1962), showed that nicotinic acid found in a liver extract could cure black tongue in dogs. Finally, this was Goldberger’s P-P factor; it was named “niacin” to avoid the connotation of cigarettes and tobacco with the phrase “nicotinic acid.” Later, vitamin B<sub>3</sub> became a synonymous name for niacin. It might be noted that Elvehjem originally referred to niacin as vitamin G, in honor of Joseph Goldberger.

There are a variety of book-length sources on the history of pellagra, and particularly on Joseph Goldberger’s work in finding a cause and a cure. Four such titles are given below, with the edited volume by Milton Terris providing many of Goldberger’s original writings on the topic of pellagra:

Milton Terris (1964). *Goldberger on Pellagra*. (Louisiana State University Press, Baton Rouge).

Elizabeth W. Etheridge (1972). *The Butterfly Caste: A Social History of Pellagra in the South*. (Greenwood Publishing Company, Westport, Connecticut).

Daphne Roe (1975). *A Plague of Corn: The Social History of Pellagra*. (Cornell University Press, Ithaca, New York).

Alan M. Kraut (2003). *Goldberger’s War: The Life and Work of a Public Health Crusader*. (Hill and Wang, New York).

## **Part III**

# **MEDICAL/INDUSTRIAL PRODUCT DISCOVERY**

## Chapter 24

# Alfred Nobel and the Nineteenth Century Development of Explosive Substances

For my part, I wish all guns with their belongings ... could be sent to hell, which is the proper place for their exhibition and use.

— Alfred Nobel (1833–1896)

The development of gunpowder during the late Tang dynasty extending from 618 to 907, is considered one of the “Four Great Inventions of China,” with the other three being paper-making, print-making, and the compass. In attempting to make an elixir guaranteeing immortality, Chinese alchemists inadvertently found that a mixture of sulphur, charcoal, and saltpeter (potassium nitrate) could produce an explosion. One might refer to this as the “mother of all surprising observations.” It led directly to various conjectures of possible usage, and eventual implementation in weapons of warfare throughout Asia and then Europe. Gunpowder was historically the first explosive to be developed, but all that would change in the Nineteenth Century.

Somewhat akin to how how gunpowder was discovered, two other

well-known explosives were initially identified through “surprising observations” based on chance explosions. The first to be discussed is guncotton (or nitrocellulose); the second is nitroglycerin which would eventually lead to the invention of dynamite by Alfred Nobel. The story begins in 1846 with nitrocellulose and a “surprising observation” produced by Christian Schoenbein (1799–1868), then teaching chemistry at the University of Basel. As the legend is usually told, Schoenbein was experimenting in his home kitchen with the distillation of sulfuric and nitric acid on the hot stove. The flask containing the two acids accidentally broke, spilling its contents on the kitchen table. Schoenbein quickly used his wife’s cotton apron to clean up the spill, and after washing it out with water, hung the apron up next to the stove. Within a short period of time, the apron exploded leaving only a small amount of residual ash. This unplanned event provided the necessary “surprising” circumstance for the subsequent development of guncotton as a commercial explosive and viable replacement for gunpowder.

In a manner similar to the discovery of guncotton, nitroglycerine was identified in 1847 by the Italian chemist Ascanio Sabrero (1812–1888) working at the University of Turin. Sabrero had earlier been a student of Théophile-Jules Pelouze in Paris who was aware of guncotton production and how sulfuric and nitric acids figured prominently in its construction. Following this lead Sabrero inadvertently developed nitroglycerine in a related way by adding glycerol to a mixture of nitric and sulfuric acids. This mixture was extremely unstable, and on one occasion exploded, badly scarring Sabrero through glass shards that embedded in his face and extremities. Sabrero viewed nitroglycerine as much too dangerous to have any practical use and

is quoted as saying: “When I think of all the victims killed during nitroglycerine explosions, and the terrible havoc that has been wreaked, which in all probability will continue to occur in the future, I am almost ashamed to admit to be its discoverer.”

The primary protagonist in this chapter, Alfred Nobel (1833–1896), also studied under Pelouze in Paris, where he presumably learned about both nitroglycerin and guncotton. Nobel was intrigued with the explosive as a means of resuscitating his family’s fortunes, and began to experiment with the material in a defunct armaments factory owned by his family. First, realizing he needed to control the sensitivity of nitroglycerin, Nobel devised a small wooden detonator with a small black powder charge placed in a metal container full of nitroglycerin, that could be ignited at the appropriate time. Later in 1865, Nobel invented an advanced blasting cap containing mercury fulminate, which was a more precise method for igniting a stock of nitroglycerin. Despite these precautions, horrendous accidents commonly occurred. For example, at one time during this early period Nobel’s entire factory blew up, killing his younger brother, Emil, as well as several other factory workers.

A turning point occurred in 1867 when Nobel had his most significant “surprising observation.” He noticed that nitroglycerine leaking through their metal containers had all been absorbed completely into the surrounding inert packing material made of diatomaceous earth. This packing material was called *kieselguhr* in German, and was found in abundance in the vicinity of Nobel’s factory. But most importantly, the absorbed nitroglycerine was much easier and safer to handle. It needed an explicit blasting cap to be detonated, thus

preventing unexpected explosions when due care was taken with the absorbed nitroglycerine. The resulting explosive product was called dynamite; it made an incredible fortune for Nobel and his family.

Besides the two important discoveries involving the ignition cap and dynamite, Nobel also developed blasting gelatin. At one point in 1875, Nobel severely cut his hand and applied as was common at the time, a collodion dressing made of nitrocellulose dissolved in ether and alcohol. Recognizing quickly (“a surprising observation”) that a mixture of nitroglycerine and collodion would provide a pliable alternative to dynamite, Nobel had a third significant invention that he called gelignite. This product was relatively free of explosion risk from impact or friction, was water resistant, and could be easily molded into whatever shapes and crevices were needed. Other explosive variations were tried later such as ballistite but the two products of dynamite and blasting gelatin remained ascendant for many years.

In 1895, Alfred Nobel developed *angina pectoris*, a heart condition treated ironically with nitroglycerin tablets placed under a patient’s tongue. He died of a cerebral hemorrhage at his villa in San Remo, Italy, in 1896. Prior to his death in November of 1895, Nobel had constructed a will authorizing the now famous Nobel prizes that are awarded to this day. Part of Nobel’s Testament for the will follows:

#### TESTAMENT

I, Alfred Bernhard Nobel, Hereby declare, after due consideration, that this is my last will with regard to the estate that, at my death I will leave behind ...

All of my remaining property shall be handled as follows:

The capital, which is to be invested by the executors in stable securities, shall constitute a fund, the annual interest on which shall

be awarded as prizes to those persons who during the previous year have rendered the greatest services to mankind. The interest shall be divided into five equal parts. One part shall be awarded to the person who has made the most important discovery or invention in the realm of physics; one part to the person who has made the most important chemical discovery or improvement; one part to the person who has made the most important discovery in the realm of physiology or medicine; one part to the person who has produced an outstanding work of literature in an ideal direction; one part to the person who has done the most and best work for the brotherhood of nations and the abolishment or reduction of standing armies as well as for the establishment and spread of peace congresses.

The prizes for physics and chemistry shall be awarded by the Swedish Academy of Sciences; those for achievements in the realm of physiology or medicine by the Karolinska Institute in Stockholm; those for literature by the Stockholm Academy; and those for the promoters of peace by a committee of five persons to be selected by the Norwegian Storting. It is my express wish that the prizes be distributed without regard to nationality, so that the prizes may be awarded in every case to the worthiest, whether he be Scandinavian or not.

Paris, the 27th of November 1895  
Alfred Bernhard Nobel

Although possibly apocryphal, some have argued that a mix-up in obituaries actually caused Alfred Nobel to form the ongoing prizes in his name. In 1888, Alfred's brother, Ludvig, died in France, but a mistaken obituary was given instead for Alfred which noted that *Le marchand de la mort est mort* (in English, the merchant of death is dead). Apparently, this bothered Alfred so much that he formed the Nobel Prizes to partially assuage any negative reputation after his death.



There are several book-length sources that tell in various levels of detail Alfred Nobel's life story, and how his famous explosives were developed. Three are mentioned here with the first being a complete biography translated from the original Swedish:

Kenne Fant (1992). *Alfred Nobel: A Biography*. (Arcade Publishing, New York.)

The two sources listed next are general historical reviews of the complete field of explosives:

G. I. Brown (1998). *The Big Bang: A History of Explosives*. (Sutton Publishing Limited, Phoenix Mill, Michigan.)

Stephen R. Brown (2005). *A Most Damnable Invention: Dynamite, Nitrates, and the Making of the Modern World*. (Thomas Dunne Books, New York.)

## Chapter 25

# Brief Tales of Medical/Industrial (Product) Discovery Involving Abductive Reasoning

Discovery needs luck, invention, intellect — none can do without the other.  
— Johann Wolfgang Goethe (1749–1832)

The discovery narratives presented in this book typically involve some collection of “surprising” observations eliciting an abductive conjecture that when fleshed out leads to the particular discovery under discussion. So, for example, the “surprising” and general observation that soil and the microbes it contains is able to decompose all forms of organic matter, led Selman Waksman to first implicitly form an abductive hypothesis that soil microbes effect this decomposition through various substances they produce. By a systematic search through soil samples and disease entities, Waksman and colleagues could identify a number of microbial forms able to generate antibiotics effective against a number of diseases. The important antibiotic streptomycin, which proved active against tuberculosis, was found in this way.

Even when the discovery process was initially based on extensive

search and testing without an obvious initial stimulating observation, there still may be some type of auxiliary but unusual circumstance that led to an eventual endpoint of importance. A good illustration was in the development of the class of sulfa drugs. Through an extensive but more-or-less blind search process, Gerhard Domagk was able to identify the first effective sulfa drug named Prontosil. But it was a French team led by Daniel Bovet at the Pasteur Institute in Paris that identified the central active sulfa component through the “surprising” observation that an old off-patent chemical called sulfanilamide could do just as well in animals as the patented Prontosil.

The various parts of this chapter briefly present a collection of abductive reasoning examples in the development of several industrial and consumer products with extensions to include a few medical devices and instruments. These small snippets are short but generally include references that could be followed up by the interested reader. What we do not present are any discoveries or inventions that occur solely by “accident,” without needing further abductive extrapolation or development. There are numerous examples for these types of serendipitous discoveries (or maybe better, flukes) that come to mind: post-it notes, silly putty, teflon, viagra, and vaseline, to name just a few.

### **The Development of Gas Lighting (1792)**

William Murdoch (1754–1839) was a Scottish inventor and engineer who worked with James Watt (1736–1819) and Matthew Boulton (1728–1809) on the development of steam engines for use in mining and in various forms of locomotion and propulsion both on land and in the water. Our interest in Murdoch, however, is in his role

as a major force behind the worldwide adoption of gas lighting both residentially and municipally, until the use of gas was overtaken by electric lighting in the late 1800s to early 1900s.

According to the 2003 text by Janet Thomson, *The Scot Who Lit the World: The Story of William Murdoch, Inventor of Gas Lighting*, the precipitating “surprise” observations occurred around 1792:

... But legend has it that, as he sat smoking his pipe by the fireside in Redruth, Cornwall, he took a tiny piece of burning coal from the fire, placed it inside the bowl and, having closed the lid, set alight the fine jet of gas issuing from the stem. Once his curiosity had been ignited, he managed to find time despite long working hours and frequent travel between mines, to experiment on the combustible properties of coal, peat, wood and other flammable substances.

...

An old friend of Murdoch’s sons recounted many years later the events of one day when Murdoch was carrying out gas light experiments in this workshop ... Not unusually some boys had gathered outside hoping to witness the strange goings on. One of them was sent by Murdoch to go and bring back a thimble. Returning with the thimble he entered the workshop and became witness to the wonders that followed. Murdoch made small perforations in the crown of the thimble which he fixed to a small pipe. He attached this pipe to the apparatus containing heated coals then lit the gas which burned in steady jets as it escaped through the holes made in the thimble.

Murdoch illuminated his own home sometime before 1794 after carrying out various experiments to determine the best way of producing the illuminating gas from coal heated in a retort or oven.<sup>1</sup>

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<sup>1</sup>Although not used for lighting but for heating and cooking, gas produced from coal

## The Invention of the Stethoscope (1816)

In September of 1816, the physician René Laennec (1781–1826) was walking through the courtyard of Le Louvre Palace in Paris when he observed a “surprising” children’s game which would eventually lead to his invention of the stethoscope. Two children were sending signals to each other using a long piece of wood and a pin. An ear placed at one end of the log could hear an amplified sound of the pin scratching the other. Soon after Laennec witnessed this game, he attended to a young but apparently very fat woman with symptoms of a diseased heart. Laennec was reluctant to engage in any diagnostic activity that might involve direct auscultation [listening] through the placement of his ear directly on her chest. As he wrote much later in his classic treatise *De l’Auscultation Médiante* [indirect listening] (as translated from the French by John Forbes in 1834):

I recalled a well known acoustic phenomenon: if you place your ear against one end of a wood beam the scratch of a pin at the other end is distinctly audible. It occurred to me that this physical property might serve a useful purpose in the case I was dealing with. I then tightly rolled a sheet of paper, one end of which I placed over the precordium (chest) and my ear to the other. I was surprised and elated to be able to hear the beating of her heart with far greater clearness than I ever had with direct application of my ear. I immediately saw that this might become an indispensable method for studying, not only the beating of the heart, but all movements [cap]able of producing sound in the chest cavity.

Besides being a physician, Laennec was an accomplished musician, 

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was a fixture in the author’s childhood in Duluth, Minnesota. Sometime in the late 1950s, natural gas from the southern United States replaced the gas produced locally from coal. If I remember correctly, this change-over necessitated a refitting of the various gas apertures because of pressure differences in the transportation of natural gas as opposed to that generated from coal.

well-versed at carving his own wooden flutes. Soon after deploying the rolled-up piece of paper to listen to the chest sounds in his overweight female patient, Laennec produced the first stethoscope from a hollow wooden cylinder fitted with both a larger ear-piece and a similar funnel-like attachment placed directly on the chest. Laennec named his stethoscope device after the two Greek words of “stethos” [chest] and “skopos” [examination]. He coined the phrase *mediate auscultation* [indirect listening] as opposed to *immediate auscultation* [direct listening], that involved the direct placement of the ear against the chest.

By means of his stethoscope and follow-up autopsies, Laennec was able to correlate the chest sounds being heard with specific pathological changes occurring in the patient. Among other conditions, tuberculosis of the lung was one prominent disease diagnosable through chest sounds. The various observations made with the stethoscope and the conditions verified by autopsy led to the Laennec masterpiece, *On Mediate Auscultation*, mentioned earlier. Laennec himself died of tuberculosis in 1826 at the age of 45, diagnosed by his physician nephew using Laennec’s own stethoscope.

Some years before Laennec’s invention of the stethoscope the Austrian physician, Leopold Auenbrugger (1722–1809), developed the technique of percussion as a diagnostic tool. By placing an ear directly on the chest of a patient and tapping, an assessment could be made of the density of the underlying tissues, and, in turn, to identify signs of disease. Auenbrugger published his observations in a short book written in Latin in 1761; the English title would read as follows: “A New Discovery that Enables the Physician From the Percussion

of the Human Thorax to Detect the Diseases Hidden Within the Chest.” Auenbrugger supposedly learned the percussive diagnostic method from his “surprising” observation of workers in the cellars of his father’s hotel determining the amount of wine left in a cask by tapping around the top of the cask as it lay on its side.

### **Mauveine (Mauve), The First Commercial Synthetic Organic Dye (1856):**

William Henry Perkin (1838–1907) started his career in science in 1853 under the organic chemist August Hofmann (1818–1892) at what is now Imperial College London. Hofmann tasked Perkin with an attempt to synthesize quinine from a chemical derived from coal-tar called aniline that had been isolated in the 1820s. During the Easter vacation period in 1856, Perkin carried out some further experimentation with aniline in a crude laboratory he had constructed in his top floor apartment in East London. There he made several “surprising” observations that would eventually stimulate a vast synthetic dye industry and revolutionize the textile industry first in England and then later and more extensively in Germany. As seen in several other chapters, the synthetic dye industry would prove crucial in a number of other medically related areas; for example, there is the development of the first sulfa drug Prontosil from the base of an azo dye, and Paul Ehrlich’s search for “magic bullets” from dyes such as methylene blue and trypan red.

In Perkin’s experimentation with aniline, he discovered that it could be partly transformed into a crude substance that when extracted with alcohol would leave a material with an intense purple color. Given the then popularity of the color purple among European

royalty and society more generally, Perkin was soon able to commercialize the patent he received in 1856 for the process of producing his more affordable but synthetic purple dye. Queen Victoria, for one, wore Perkin's mauve color to her daughter's wedding in 1858.<sup>2</sup>

### **The Discovery of Stainless Steel (1912):**

In 1912 and before the onset of the First World War, Harry Brearley (1871–1948) was working as a metallurgist for the Brown-Firth Laboratories in Sheffield, England. Brearley was given the job of finding a steel alloy containing various amounts of carbon, chromium, and other substances that would be less prone to excessive wear and erosion when used for the internal surface of gun barrels. The various experimental alloys produced would be polished and etched to study their respective microstructures, and then placed in a discard pile. After some number of weeks studying and amassing the experimental samples, Brearley made a crucial “surprising” observation with respect to one of the discarded prototypes — it still appeared “like new” with no signs of corrosion or erosion.

Upon further examination, the pristine experimental alloy was made of a unique combination of chromium and carbon, which is now universally called “stainless steel.” Brearley first took his alloy to the extensive Sheffield cutlery market where it found immediate success. It was not damaged easily as were cheaper steel utensils, and importantly was more affordable than the use of expensive silver. Brearley received U.S. and Canadian patents for stainless steel in

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<sup>2</sup>The story of Perkin's discovery is told with some flair in Simon Garfield's *Mauve: How One Man Invented a Color that Changed the World* (2000; W. W. Norton & Company, New York).



1915 using as part of the patent application the following declarative statement:

My invention relates to the production of steel or steel alloys and has for its object to produce a malleable steel which shall be practically untarnishable and can be forged, rolled, hardened and tempered under ordinary commercial conditions ... that the addition to iron of an amount of chromium between 9 and 16%, and also an amount of carbon not greater than 0.7%, will produce such a product.

Brearily teamed up with a fellow metallurgist named Elwood Haynes (1857–1925) to form the American Stainless Steel Company in the 1920s. By 1929, over 25,000 tons of stainless steel were being produced annually. Various iconic structures were soon designed with stainless steel in mind; for example, the Chrysler Building in New York opened in 1930 clad in a stainless steel helmet. Similarly, the iconic Gateway Arch in St. Louis, designed by the architect Eero Saarinen and opened in 1965, has a stainless steel casing surrounding the complete structure.<sup>3</sup>

### **The Hook-and-Loop Fastener (“Velcro”) (1941)**

Georges de Mestral (1907–1990) was a Swiss electrical engineer who invented the now familiar hook-and-loop fastener called Velcro. Mestral was an avid hunter and hiker, and one day in 1941 came back from such an outing with cockleburs stuck all over both his trousers and his dog’s fur. These “surprising” observations led Mestral to the abductive conjecture that some type of adhesive system was present in the cocklebur to allow for such a clinging property. Viewing the

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<sup>3</sup>A thorough telling of the discovery of stainless steel and the aftermath is given in the 2010 text by Harold M. Cobb, *The History of Stainless Steel* (ASM International, Materials Park, Ohio).

cocklebur microscopically, Mestral discovered a large collection of hook-like shapes that were able to attach to both clothing and fur, among other surfaces. This conjecture and observation started Mestral on his search for a two-sided fastener – one side had stiff “hooks” comparable to the burrs on the cocklebur; the other side had softer “loops” similar to what could be seen in fabric.

After some ten years of experimentation, Mestral settled on nylon which when sewn under hot infrared light formed loops. He also fashioned a process to snip off the heads of the loops to form the necessary hooks. This two-sided hook-and-loop fastener was patented in 1955 under the trademarked name of “Velcro,” taken from the two French words of “velour” (or “velvet”) and “crochet” (or “hook”).

### **Intraocular Lens Replacement (1949)**

In August of 1940 during World War II, the English ophthalmologist Harold Ridley (1906–2001) was called upon to tend to the eye injuries incurred by a Royal Air Force Squadron leader, Gordon Gleaver. Gleaver had inadvertently forgotten his flight goggles when scrambling for an emergency mission. During the ensuing flight his Hurricane fighter aircraft was hit with machine-gun fire causing Gleaver’s plane to burst into flames, sending acrylic shards from the shattered canopy into his eyes. Gleaver was nevertheless able to turn his airplane upside down and safely parachute to the ground.

Gleaver’s right eye was too badly damaged to save, but he recovered sight in the left after undergoing several surgeries. At this point Ridley noted several “surprising” circumstances: first, the plastic splinters in Gleaver’s left eye had no apparent effect on his sight; and second, there was no attempt by his body to reject the implanted

shards. But it would not be until 1948 that Ridley would finally draw from this initial observational evidence the abductive conjecture that it would be possible to replace a cataract removed from someone's eye with a plastic intraocular lens that could serve as a replacement for a natural lens and yet not be rejected by the recipient's body.

The impetus for Ridley's realization was supposedly from a student witnessing Ridley removing a patient's cataract who commented "It's a pity you can't replace the cataract with a clear lens." The story of Ridley's development of the intraocular lens, including this quote, is told more completely by Robert W. Winter in *Accidental Medical Discoveries* (Chapter 5: the Artificial Lens: A legacy of Wartime).

To produce a suitable intraocular plastic lens professionally, Ridley contacted an optical scientist, John Pike, who worked at a firm called Rayner, a maker of optical devices. Pike fashioned a lens out of a purer variety of the same type of plastic that was still embedded in Gleaver's eye. In November of 1949, Ridley removed the cataract from a forty-five year old woman volunteer and three months later implanted the plastic lens. Although Ridley kept somewhat quiet about this initial patient and several others so that he could see how they progressed over a period of time, word somehow still got out. The older English ophthalmology establishment rose up in opposition to such a reckless procedure. The current author and millions just like him offer proof that such resistance was eventually overcome.

There is one more relevant topic about cataract surgery that has a basis in abductive reasoning. In the mid 1960s, a young eye surgeon, Charles Kelman (1930–2004), was having some dental work done when his dentist touched his teeth with an ultrasonic probe that

produced extremely fast vibrations along with a high-pitched sound. At this moment Kelman conjectured that the “surprising” effects of the ultrasonic probe could be used to liquify the eye lens and extract it through a fine incision made in an eye. After several years of work, Kelman perfected the process of phacoemulsification where the tip of an ultrasonic probe is inserted through a small incision in an eye. The vibrating probe liquifies the lens allowing extraction through the small tiny incision. A plastic folded lens is then inserted through the same small incision. Upon unfolding, the plastic lens then provides an artificial replacement for the emulsified and extracted lens.<sup>4</sup>

## **Osseointegration and Dental Implantology (1952)**

Osseointegration refers to the seamless biological fusion of bone to a foreign material, which is typically the metal titanium. It was so named by the Swedish physician, Per-Ingvar Brånemark (1929–2014), based on some “surprising” observations he made in the early 1950s about the experimental apparatus he was using to study blood cell regeneration in bone marrow. Brånemark had surgically implanted a small optical chamber into a rabbit’s femur that was made from titanium on the advice of an orthopedist surgeon who studied different metals for hip prostheses. However, after the conclusion of the study, the titanium chamber placed into the lower bones of the rabbit could not be removed. The bone and optical chamber had seamlessly become one entity. Based on this unusual situation, Brånemark abductively conjectured the phenomenon of osseointegration.

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<sup>4</sup>Those of us who have had cataract surgery can attest to the general “creepiness” of the lens emulsification which is done only under a light anesthetic.

Although the phenomenon of osseointegration had been noted in passing several times prior to Brånemark's work, it was he who coined the term for this unusual formation of a direct interface between an implant and bone without any intervening soft tissue. Brånemark continued to study the osseointegration process generally, and then later more specifically in dental implants. In 1965 Gösta Larsson (1931–2006) became the first recipient of a modern dental implant. Because Larsson had no teeth of his own, Brånemark installed four titanium implants that could be then used to hold a removable denture. Larsson relied on these implants until his death some forty years after their installation. This first patient opened a new area in dentistry called dental implantology with Brånemark rightly considered its father.

The use of titanium dental implants by Brånemark was severely criticized by his European dental contemporaries, most likely because he was not trained as a dentist but rather as a physician. It wasn't until a conference organized in Toronto in 1983 by George Zarb from the University of Toronto that implantology became an acceptable practice worldwide. It might be noted that the present author can personally attest to the process of osseointegration and to the durability of titanium dental implants.

## **Gene Editing Through CRISPR (2000s)**

One of the most significant medical/industrial discoveries of the last one hundred years or so is a method for editing the genetic structure of living organisms called CRISPR (pronounced as “crisper,” referring to the compartment at the bottom of a refrigerator used for storing fruits and vegetables). The 2020 Nobel Prize in Chemistry

went to two women, Emmanuelle Charpentier and Jennifer Doudna, “for the development of a method for genome editing.” The summary statement from the press release from the Nobel Committee follows:

Emmanuelle Charpentier and Jennifer A. Doudna have discovered one of gene technology’s sharpest tools: the CRISPR/Cas9 genetic scissors. Using these, researchers can change the DNA of animals, plants and microorganisms with extremely high precision. This technology has had a revolutionary impact on the life sciences, is contributing to new cancer therapies and may make the dream of curing inherited diseases come true.

Although Charpentier and Doudna were the named Nobel Prize recipients in 2020, the basis for their “genetic scissors” goes back to the 1990s and the graduate student work of Francisco Mojica (1963–), carried out at the University of Alicante in Spain. Mojica was studying microbes called archaea which are bacteria-like single-celled organisms that lack nuclei. He was particularly interested in one type of archaea called *Haleferex mediterranei* which was able to survive in the hypersaline waters of Santa Pola near the town of Alicante. Mojica proceeded to sequence the DNA extracted from his preferred species, using the usual letters of A, G, C, and T to denote the four possible chemical subunits along the DNA molecule. Based on the generated DNA sequencing, Mojica made the first of several “surprising” observations that would later lead to the construction of a “genetic scissors.”

In his obtained DNA sequencing, Mojica observed the same thirty-letter sequence repeated fourteen times with separations of what seemed at the time to be random letters not corresponding to any

known genetic structures. He called these separations “spacers.” In the large open DNA databases then available, Mojica found that the strange repetitive sequences were also present in many other organisms including the bacteria that causes tuberculosis and the plague. As a way of referring to these repeated sequences, Mojica coined the phrase “Clustered Regularly Interspaced Short Palindromic Repeats,” or the familiar acronym of CRISPR, for short.

As noted in the chapter on the discovery of viruses, a “phage” is a particular kind of virus that for it to reproduce must invade a bacterium and inject its genetic material inside the cell. This process results in multiple new phages all having the same structure as the initial phage. These new entities eventually burst the cell wall, destroying the bacterium itself. To survive the phage onslaught, bacteria have developed a range of defenses, with one involving the “spacers” present in the bacteria’s genetic structure. This was discovered by Mojica through yet another set of “surprising” and fortuitous observations. Using the common *E. Coli* bacteria as a model, Mojica turned his efforts toward the “spacer” sequences and found to his amazement that an exact match between an *E. Coli* spacer sequence and a phage, called P1, which was known to attack the bacteria. Moreover, the particular bacterial strain used by Mojica was completely resistant to P1. In other words, and as an explanatory abductive conjecture, the spacers seemed to provide an immunity against those phages when their DNA sequences matched, allowing the bacteria to “remember” the phages it has encountered previously, and presumably to destroy them before the bacteria could be infected. Using various other bacteria and archaea, Mojica worked through the DNA sequences for some 4,500 different spacers. Many of

the sequences Mojica studied contained DNA sections that matched those of phages, suggesting that they formed a system of innate microbial immunity. After many rejections, Mojica was finally able to publish his results in early 2005 in the *Journal of Molecular Evolution*.

The next major development in evaluating CRISPR as being a type of adaptive immune system is due to Rodolphe Barrangou, working with the bacterial starter cultures for the yoghurts produced by the company Danisco, a subsidiary of DuPont. Rather incredibly, Danisco had amassed over several decades a frozen archive of all their commercial starter strains of bacteria as well as of the phages that caused difficulty for their cultures. Because of this extensive library, Barrangou had available three crucial sources of evidence: strains of bacteria before having difficulty with a particular phage; strains of bacteria that were still able to grow after a phase encounter; and a sample of the specific phage in question. Based on this available information, Barrangou made a crucial but “surprising” observation: phage resistant bacteria had parts of the phage DNA incorporated into their own DNA where it had not been before. And somewhat conversely, bacteria that did not develop a resistance, did not have the incorporated phage sequence. Based on these results, an implicit abductive conjecture was made for the presence of an immune system where the DNA from an encountered phage was stored in the spacers between the repetitive sequences.

The immunity process against phages used by bacteria proceeds with a CRISPR associated protein (an enzyme called “Cas9”). It is as if Cas9 carried a “most wanted poster” chosen from the spacer



sequences that contain the same signature gene orderings for the attacking phages. Once located the Cas9 enzyme acts as a scissors to cut the invading phage, rendering it harmless. The trick to harness this immunity process into a general gene-editing tool was to figure out how to feed the Cas9 enzyme the particular gene sequences to be cut. Successful completion of that task led to the 2020 Nobel Prize for Doudna and Charpentier.

As noted, the process of developing a viable gene-editing procedure from the initial “surprising” observations of Mojica and Barrangou led to the 2020 Nobel Prize in Chemistry for Doudna and Charpentier; this story is told in several sources:

Jennifer A. Doudna and Samuel H. Sternberg (2017), *A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution* (Harper Collins Publishers, Boston).

Walter Isaacson (2021), *The Code Breaker: Jennifer Doudna, Gene Editing, and the Future of the Human Race* (Simon & Schuster, New York).

Tom Ireland (2023), *The Good Virus: The Amazing Story and Forgotten Promise of the Phage* (In particular, see Chapter 14: An Ancient Technology) (W. W. Norton & Company, New York).

**Part IV**

**SCIENTIFIC DISCOVERY**

## Chapter 26

# Brief Tales of Scientific Discovery Involving Abductive Reasoning

A fool sees not the same tree that a wise man sees.

— William Blake (1757–1827)

The scientific discoveries presented in this chapter all start with the typical abductive structure: there is some initial “surprising” observation or circumstance that leads to the formulation of an explanatory abductive hypothesis. But for scientific discovery there is usually a need to go much beyond a first basic conjecture and “flesh out” a complete principle or law. An obvious illustration of the latter would be in the formulation of Newton’s theory of universal gravitation that began with the observation of a simple fall of an apple from a tree directly to the ground. The other illustrations given in this chapter generally need similar elaborations from a first “bare-bones” abductive hypothesis that would account for the initial and stimulating “surprising” observation(s).

**Archimedes of Syracuse and the Golden Crown (287–212 BCE)**

Archimedes was an ancient Greek mathematician/scientist, considered by many to be the greatest mathematician from antiquity as well as one of its most prominent scientists and inventors. Archimedes, for example, formulated the physical law of buoyancy (called Archimedes' Principle), which states that any body partially or completely submerged in a fluid, whether gas or liquid, is acted upon by an upward force of a magnitude equal to the weight of the fluid displaced by the body. Thus, a boat launched into water sinks to the depth where the weight of the displaced water is equal to the weight of the boat.

Our interests are not in Archimedes' Principle itself but in a related notion that the volume of an irregular solid object that sinks may be determined by the amount of fluid displaced. According to legend, Archimedes came to this (abductive) conjecture from the "surprising" observation that when he stepped into a bath, the water level rose according to the volume of the body part submerged. On this realization that the volume of an irregular solid object could be measured by the amount of water it displaced, Archimedes is said to have leapt out of the bath and proceeded to run naked through the streets of Syracuse shouting "Eureka" (from the Greek word meaning "I have found it").

Again according to legend, the revelation Archimedes had in his bath was a way to answer his king's request to determine if a crown was pure gold or adulterated with some other metal. This story will be told through an excerpt entitled "Eureka!" from James Baldwin's, *Thirty More Famous Stories Retold*, written in 1905:

There was once a king of Syracuse whose name was Hiero. The country over which he ruled was quite small, but for that very reason

he wanted to wear the biggest crown in the world. So he called in a famous goldsmith, who was skillful in all kinds of fine work, and gave him ten pounds of pure gold.

“Take this,” he said, “and fashion it into a crown that shall make every other king want it for his own. Be sure that you put into it every grain of the gold I give you, and do not mix any other metal with it.”

“It shall be as you wish,” said the goldsmith. “Here I receive from you ten pounds of pure gold; within ninety days I will return to you the finished crown which shall be of exactly the same weight.”

Ninety days later, true to his word, the goldsmith brought the crown. It was a beautiful piece of work, and all who saw it said that it had not its equal in the world. When King Hiero put it on his head it felt very uncomfortable, but he did not mind that — he was sure that no other king had so fine a headpiece. After he had admired it from this side and from that, he weighed it on his own scales. It was exactly as heavy as he had ordered.

“You deserve great praise,” he said to the goldsmith. “You have wrought very skillfully and you have not lost a grain of my gold.”

There was in the king’s court a very wise man whose name was Archimedes. When he was called in to admire the king’s crown he turned it over many times and examined it very closely.

“Well, what do you think of it?” asked Hiero.

“The workmanship is indeed very beautiful,” answered Archimedes, “but — but the gold — ”

“The gold is all there” cried the king. “I weighed it on my own scales.”

“True,” said Archimedes, “but it does not appear to have the same rich red color that it had in the lump. It is not red at all, but a brilliant yellow, as you can plainly see.”

“Most gold is yellow,” said Hiero; “but now that you speak of it I do remember that when this was in the lump it had a much richer color.”

“What if the goldsmith has kept out a pound or two of the

gold and made up the weight by adding brass or silver?" asked Archimedes.

"Oh, he could not do that," said Hiero; "the gold has merely changed its color in the working" But the more he thought of the matter the less pleased he was with the crown. At last he said to Archimedes, "Is there any way to find out whether that goldsmith really cheated me, or whether he honestly gave me back my gold?"

"I know of no way," was the answer.

But Archimedes was not the man to say that anything was impossible. He took great delight in working out hard problems, and when any question puzzled him he would keep studying until he found some sort of answer to it. And so, day after day, he thought about the gold and tried to find some way by which it could be tested without doing harm to the crown.

One morning he was thinking of this question while he was getting ready for a bath. The great bowl or tub was full to the very edge, and as he stepped into it a quantity of water flowed out upon the stone floor. A similar thing had happened a hundred times before, but this was the first time that Archimedes had thought about it.

"How much water did I displace by getting into the tub?" he asked himself. "Anybody can see that I displaced a bulk of water equal to the bulk of my body. A man half my size would displace half as much."

"Now suppose, instead of putting myself into the tub, I had put Hiero's crown into it, it would have displaced a bulk of water equal to its own bulk. Ah, let me see! Gold is much heavier than silver. Ten pounds of pure gold will not make so great a bulk as say seven pounds of gold mixed with three pounds of silver. If Hiero's crown is pure gold it will displace the same bulk of water as any other ten pounds of pure gold. But if it is part gold and part silver it will displace a larger bulk. I have it at last! Eureka! Eureka!"

Forgetful of everything else he leaped from the bath. Without stopping to dress himself, he ran through the streets to the king's

palace shouting, “Eureka! Eureka! Eureka!” which in English means, “I have found it! I have found it! I have found it!”

The crown was tested. It was found to displace much more water than ten pounds of pure gold displaced. The guilt of the goldsmith was proved beyond a doubt. But whether he was punished or not, I do not know, neither does it matter.

...

## **Newton’s Law of Universal Gravitation (1666)**

Isaac Newton (1642–1726) is regarded as one of the greatest physicists/mathematicians of all time. Although known for a large number of mathematical and physical theories and laws, the concern here will only be in his law of universal gravitation that may be stated succinctly as follows:

... every particle in the universe attracts every other particle with a force proportional to the product of their masses and inversely proportional to the square of the distance between their centers. Separate objects attract and are attracted as if all their masses were concentrated at their centers.

As the famous legend is usually told, Newton began his formulation of the law of universal gravitation by witnessing the fall of an apple from a tree. Newton had just obtained his BA degree in 1665 from Trinity College, Cambridge, when the university closed down for two years as a precaution against the Great Plague of London (1665–1666). Returning to his home at Woolsthorpe Manor in the county of Lincolnshire, Newton engaged in private study and contemplation over the range of topics he is known for in both physics and mathematics.

Much later in 1752 William Stukeley (1687–1765) wrote his *Memoirs of Sir Isaac Newton's Life* in which he relates a conversation with Newton in Kensington in April of 1726, the year in which Newton died. The conversation was about the apple in the garden descending directly to the ground and not sideways or upwards, and Newton's abductive conjecture as to why this is a primitive illustration of the universal law of gravitation:

... after dinner, the weather being warm, we went into the garden, & drank thea [sic] under the shade of some apple trees, only he, & myself. amidst other discourse, he told me, he was just in the same situation, as when formerly, the notion of gravitation came into his mind. "why should that apple always descend perpendicularly to the ground." thought he to himself: occasion'd by the fall of an apple, as he sat in a contemplative mood: "why should it not go sideways, or upwards? but constantly to the earths [sic] centre? assuredly, the reason is, that the earth draws it. there must be a drawing power in matter. & the sum of the drawing power in the matter of the earth must be in the earths [sic] center, not in any side of the earth. therefore dos [sic] this apple fall perpendicularly, or toward the center. if matter thus draws matter; it must be in proportion of its quantity. therefore the apple draws the earth, as well as the earth draws the apple."

...

That there is a power like that we here call gravity which extends its self thro' the universe ... & thus by degrees, he began to apply this property of gravitation to the motion of the earth, & of the heavenly bodys [sic]: to consider their distances, their magnitudes, their periodical revolutions: to find out, that this property, conjointly with a progressive motion impressed on them in the beginning, perfectly solv'd their circular courses; kept the planets from falling upon one another, or dropping all together into one center. & thus he unfolded the Universe. this was the birth of those amazing



discoverys [sic], whereby he built philosophy on a solid foundation, to the astonishment of all Europe.

Although Newton lived some two-hundred years before Charles Peirce, some of Newton's writing has an echo of the idea of abductive reasoning. The quote below is from Book 3 of Newton's *Principia*. Here, read "phenomena" as "surprising observations"; "propositions" as "abductive hypotheses"; and "induction" as "elaboration" of an abductive hypothesis:

... In this [experimental] philosophy particular propositions are inferred from the phenomena, and afterwards rendered general by induction. Thus it was that the impenetrability, the mobility, and the impulsive force of bodies, and the laws of motion and of gravitation, were discovered. And to us it is enough that gravity does really exist, and act according to the laws which we have explained, and abundantly serves to account for all the motions of the celestial bodies, and of our sea.

## **The Discovery of Oxygen and its Role in the Processes of Combustion (Late 1700s)**

Combustion is a common everyday phenomenon seen in a variety of circumstances such as in the burning of a candle or wood, the use of gasoline in running a car having an internal combustion engine, cooking on a stovetop with natural gas, or more subtly, in the respiration of all living organisms and the oxidation of various metals. Although it is now known that "combustion" is a chemical process where substances combine with oxygen present in the air to produce heat and light, that knowledge dates only from the late Eighteenth Century. Prior to that time, the abductive conjecture most

often invoked to explain the “surprising” observation(s) of combustion in its myriad forms was phlogiston theory. Formally developed by Georg Stahl (1659–1734) in the early 1700s, combustion was explained by the release of a conjectured but invisible substance called “phlogiston.” Thus, a burning candle placed under an inverted glass container (called a “pneumatic trough”) would burn until the air in the glass was “saturated” with phlogiston. Similarly, mice placed in this saturated environment would soon die because the phlogiston expelled by their respiration could no longer be absorbed. If, however, a green plant were also placed in the container and exposed to sunlight, the air could be “refreshed” thus allowing a flame to burn and a mouse to breathe.

Although a believer in phlogiston as the reason for combustion to exist, Joseph Priestley (1733–1804) would also be the initiator of the theory’s overthrow by performing several simple experiments involving an inverted glass cylinder on a floating platform. On August 1, 1774, Priestly used a lens to focus sunlight on mercury oxide (“red calx” of mercury) placed under the glass cylinder. This procedure produced a water insoluble gas that allowed a candle to burn more brightly than in the regular atmosphere; also, a mouse was able to survive four times longer than in atmospheric air captured in the inverted glass cylinder. Priestly believed that the “new air” had to have absorbed so much phlogiston that better combustion could be achieved — he called the new gas, “dephlogisticated air.” In capturing and breathing in this new gas, Priestly commented:

The feeling of it in my lungs, was not sensibly different from that of common air, but I fancied that my breast felt peculiarly light and easy for some time afterwards. Who can tell but that in time, this

pure air may become a fashionable article of luxury. Hitherto only two mice and myself had the privilege of breathing it.

In the Fall of 1794, Priestly visited in Paris the French aristocrat and scientist Antoine Lavoisier (1743–1794), and told him of his experimentation with “dephlogisticated air.” Lavoisier, being more quantitative in orientation than Priestly, and a firm believer in the conservation of mass, noted the “surprising” fact that the various calxes (oxides) weighed more than the original metals. This suggested the new abductive conjecture that combustion involved some combination with a substance from the air rather than from a loss of phlogiston. Lavoisier named Priestly’s dephlogisticated air “oxygene” after the Greek word for “acid-maker,” and recognized it as one of the chief components of the atmosphere. In effect, Lavoisier reversed the process assumed for the occurrence of combustion from one of emitting phlogiston to one of incorporating oxygen from the atmosphere which increased the weight of the resulting products of combustion.

Joseph Priestley in his 1776 discussion of the discovery of oxygen comes close to formulating how abductive conjectures can be used to explain “chance” or “surprising” observations:

The contents of this section will furnish a very striking illustration of the truth of a remark which I have more than once made in my philosophical writings, and which can hardly be too often repeated, as it tends greatly to encourage philosophical investigations: viz. that more is owing to what we call chance, that is, philosophically speaking, to the observation of events, arising from unknown causes, than to any proper design, or preconceived theory in this business.

I wish my reader be not quite tired with the frequent repetition of the word surprise, and other of similar import; but I must go on in that style a little longer. For the next day I was more surprised than ever I had been before, with finding that, after the above mentioned mixture of nitrous air and the air from *mercurius calcinatus*, had stood all night, (in which time the whole diminution must have taken place; and, consequently had it been common air, it must have been made perfectly noxious, and entirely unfit for respiration or inflammation) a candle burned in it, and even better than in common air.

I cannot, at this distance of time, recollect what it was that I had in view in making this experiment; but I know I had no expectation of the real issue of it. Having acquired a considerable degree of readiness in making experiments of this kind, a very slight and evanescent motive would be sufficient to induce me to do it. If, however, I had not happened, for some other purpose, to have had a lighted candle before me, I should probably never have made the trial; and the whole train of my future experiments relating to this kind of air might have been prevented.

## **Element Discovery Through Abductive Reasoning (Seventeenth Century and Later)**

Although many of the well-known elements such as the common metals of iron, gold, copper, and so on, have been known since antiquity, a majority of the natural elements have been identified only from the Seventeenth Century and later. Several of these more recent element discoveries can be considered the result of abductive reasoning, where some process or situation leads to a collection of “surprising” observations that can be explained and understood by the conjecture of a “new” element unknown up to that time. Three such identified substances will be briefly mentioned here: phosphorus (1669), iodine (1811), and radium (1898).

The first discovery of a previously unknown element, phosphorus, was made by Hennig Brandt in 1669. In his quest for a philosophers' stone that would transform base metals into gold, Brandt first boiled down twelve-hundred gallons of urine over a period of two weeks and then maintained the resulting mixture at the highest temperature his furnace could reach. After several hours a white vapor formed that gleamed for an extended period of time. Such a glowing substance had never been seen before, prompting Brandt to name the material, phosphorus, a Latin term for things emitting light.

The French chemist, Bernard Courtois (1777–1838), discovered iodine in 1811 while engaged in the manufacture of saltpeter used in the making of gunpowder from seaweed collected along the coasts of Normandy and Brittany. The seaweed was first burned and the ash washed with water, with the remaining waste destroyed by adding sulfuric acid. After a mistake of adding too much sulfuric acid, the “surprising observation” occurred of a cloud of vivid purple vapor that crystallized on the cold copper surfaces of the vat being used. Because Courtois lacked money for further work on the purple crystals, he gave samples to, among others, the chemist Joseph Louis Gay-Lussac (1778–1850) and André-Marie Ampère (1775–1836); Ampère in turn gave a sample to the English chemist Humphry Davy (1778–1829). Both Davy and Gay-Lussac published articles on the new element to be called “iodine,” but both acknowledged Courtois as the first to isolate the new element.

The last element discovery mentioned is that of radium by Marie and Pierre Curie. Using a device invented by Pierre and his brother to measure the level of radioactivity emitted by a substance, the “cu-

rious” observation was made that uranium ore (such as pitchblende) was more radioactive than pure samples of uranium itself. The Curies were able eventually to isolate radium from the pitchblende ore. Radium is the most radioactive natural element at several million times more active than pure uranium. Eventually, Marie Curie received the 1911 Nobel Prize in Chemistry for this work on isolating radium and the various sequela. The 1911 citation for Marie Curie reads as follows:

... in recognition of her services to the advancement of chemistry by the discovery of the elements radium and polonium, by the isolation of radium and the study of the nature and compounds of this remarkable element.

As we note in the next section, this was the second Nobel Prize for Marie Curie. Her first was awarded jointly with Pierre Curie and Henri Becquerel for the identification and general study of radioactivity.

### **Wilhelm Conrad Röntgen and the Discovery of X-Rays (1895)**

As discussed in the preface of the larger companion volume, the discovery of penicillin by Alexander Fleming in the 1920s can be considered a prime example of abductive reasoning based on an initial “surprising” observation. An even earlier example, however, of an incredibly important bit of abductive inference would be the discovery of X-rays by Wilhelm Röntgen in 1895. In much the same manner that Fleming’s work with penicillin was a precursor to the large array of available twentieth century antibiotics, Röntgen’s discovery of

X-rays led to the abundance of different imaging modalities now at the disposal of the medical community.

In November of 1895, William Röntgen was working in his home physics laboratory at the University of Würzburg in Germany with a new electrical discharge cathode ray tube invented recently by William Crookes (1832–1919), among several others. In a completely darkened room Röntgen was using a Crookes tube that was heavily shielded and completely encased with black cardboard. When an electrical discharge from the negative electrode occurred in the tube, Röntgen noticed a “surprising” occurrence some distance away. A screen coated with barium platinocyanide began to glow a bright green. Röntgen knew that any electrical discharge from the tube itself was too far away from the screen to be a direct cause of the fluorescence. So, because of this unknown source producing the glow, Röntgen named whatever it was, “X-rays.”

Over the next several weeks, Röntgen worked incessantly to discover, first of all, the substances that the newly found X-rays could pass through, such as wood and paper, and those that it could not, such as lead and other thick metals. Also, because of an inadvertent shining of X-rays on his own hand, Röntgen briefly saw part of his own internal bone structure. He regularized such a use with a photographic plate that captured an internal image of the material the X-rays had passed through. In December of 1895 he asked his wife Bertha to let him photograph her hand using his newly discovered X-rays. After a fifteen minute exposure the first “radiograph” of a human body part was generated showing clearly the bone structure of Bertha’s hand along with the two opaque rings she was wearing.

This photograph became famous almost immediately; it could be seen as marking the onset of radiology as a medical speciality.<sup>1</sup>

Although Röntgen's first manuscript on X-rays appeared in early January of 1896 in a rather obscure German periodical, it was quickly translated into English and published soon thereafter in both *Science* and *Nature* under the title, "On a New Kind of Rays." It was also covered heavily in the major newspapers of the time. Other honors were quickly bestowed on Röntgen, including the first Nobel Prize in Physics (1901) with the citation: "in recognition of the extraordinary services he has rendered by the discovery of the remarkable rays subsequently named after him." Although Röntgen did travel to Stockholm to receive the Prize, he did not deliver a customary lecture. He also donated all of the substantial Nobel Prize money to the University of Würzburg, and never sought a patent for his discovery.

### **Henri Becquerel and the Discovery of Spontaneous Radioactivity (1896)**

As were many others, Henri Becquerel (1852–1908) was intrigued by Röntgen's discovery of X-rays, and wondered whether a naturally phosphorescent uranium mineral he had been studying would by itself emit X-rays when stimulated by sunlight. In 1896, Becquerel first exposed the uranium salt called potassium uranyl sulfate to sunlight and then placed it outside of a photographic plate containing a metal cross and several other metal objects all wrapped in black paper. As Becquerel had conjectured, the developed photographic plate showed the strong images of the metallic items that had been placed under-

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<sup>1</sup>On seeing the X-ray photograph of her own hand skeleton, Bertha was reported to have exclaimed, "I have seen my death!" Röntgen himself commented, "it's unearthly, it's truly mystical."



neath the black paper, presumably from X-rays generated by the fluorescing mineral.

In attempting a replication of this imaging phenomenon, Becquerel tried to repeat the process but encountered a heavily overcast Paris day, so he merely placed the whole apparatus in a drawer and waited. After some period of time and before a repeat exposure to sunlight was performed, Becquerel fortuitously decided to develop the photographic plate. To his amazement the images were still clear and strong showing that the uranium mineral emitted radiation without any external source of excitation. In other words, Becquerel had discovered naturally occurring radioactivity, a truly “surprising” observation that led to the search for radioactivity in other minerals as well.

One of Becquerel’s doctoral students, Marie Curie, coined the term “radioactivity” for the emissions that Becquerel had fortuitously demonstrated. For her own doctoral research, Marie Curie studied the radioactivity in other minerals containing uranium, particularly in pitchblende (uranite) and chalcocite (torbernite). To measure the level of radioactivity present in any sample, she relied on an electrometer, an instrument for measuring an electric charge invented by her husband, Pierre Curie, some fifteen years earlier. In general, radioactivity creates an electric charge in the air around the sample being studied, so the level of radioactivity present could be measured directly by the electrometer.

Marie Curie produced several “surprising” observations with her use of the electrometer. One such circumstance was of pitchblende being four times as radioactive as uranium itself; chalcocite was twice

as radioactive. To Marie Curie these observations suggested two conjectures: first, the different levels of radioactivity for equal amounts of the substances being studied implied that pitchblende and chalcocite must contain other substances that are more radioactive than uranium itself. And secondly, that radioactivity is not just the result of simple molecular interaction but might somehow involve atoms not being as indivisible as then believed.

Marie Curie's husband, Pierre Curie, became increasingly intrigued by his wife's work, and finally joined her in 1898. The Curies isolated several different radioactive compounds, among these were the elements of the then known thorium and a new element to be called polonium, with the later being named for Marie Curie's native Poland. They also succeeded in obtaining a small amount of radium chloride (a tenth of a gram) from a ton of pitchblende. For Becquerel's initial identification of spontaneous radioactivity and the follow-up research by the Curies, the 1903 Nobel Prize in Physics was awarded jointly to these three individuals. The overall citation for the award was as follows:

The Nobel Prize in Physics 1903 was divided, one half awarded to Antoine Henri Becquerel "in recognition of the extraordinary services he has rendered by his discovery of spontaneous radioactivity," the other half jointly to Pierre Curie and Marie Curie ... "in recognition of the extraordinary services they have rendered by their joint researches on the radiation phenomena discovered by Professor Henri Becquerel."

The work done explicitly by Marie and Pierre Curie was described more completely as follows:

The 1896 discovery of radioactivity by Henri Becquerel inspired Marie and Pierre Curie to further investigate this phenomenon. They examined many substances and minerals for signs of radioactivity. They found that the mineral pitchblende was more radioactive than uranium and concluded that it must contain other radioactive substances. From it they managed to extract two previously unknown elements, polonium and radium, both more radioactive than uranium.

In April of 1906, Pierre Curie was killed while walking across the Rue Dauphine in Paris during a severe rainstorm. Pierre fell under a horse-drawn vehicle, and died instantly from his resulting skull fracture. Marie Curie continued on with their joint research and successfully isolated pure radium as a metal in 1910. This was a momentous discovery for the field of medicine if only for the fact that several years earlier a joint Curie paper had shown that diseased tumor forming cells were destroyed faster than healthy cells — the basis for radiotherapy as a treatment for cancer. The summary from the Nobel committee for the work that Marie Curie carried out for her second Nobel Prize in 1911 reads as follows:

After Marie and Pierre Curie first discovered the radioactive elements polonium and radium, Marie continued to investigate their properties. In 1910 she successfully produced radium as a pure metal, which proved the new element's existence beyond a doubt. She also documented the properties of the radioactive elements and their compounds. Radioactive compounds became important as sources of radiation in both scientific experiments and in the field of medicine, where they are used to treat tumors.

Marie Curie died in July of 1934 from aplastic anemia, a condition conjectured to have resulted from the long-term radiation exposure

that damaged her bone marrow. To this day, Marie Curie's original papers from the 1890s still have high levels of radioactive contamination, and for safety are kept in lead-lined boxes. Those wishing to consult these original sources must wear protective clothing. It is of some historical interest to note that evidence has existed from the early 1900s about radiation being possibly harmful to the human body. For example, Henri Becquerel himself carried a sample of a radium salt in his shirt pocket until he discovered that it badly burned part of his chest.

In commenting on the importance of the Curies' work in the *Encyclopedia Americana* (1986), L. Pearce Williams writes as follows:

The result of the Curies' work was epoch-making. Radium's radioactivity was so great that it could not be ignored. It seemed to contradict the principle of the conservation of energy and therefore forced a reconsideration of the foundations of physics. On the experimental level the discovery of radium provided men like Ernest Rutherford with sources of radioactivity with which they could probe the structure of the atom. As a result of Rutherford's experiments with alpha radiation, the nuclear atom was first postulated. In medicine, the radioactivity of radium appeared to offer a means by which cancer could be successfully attacked.

In experimenting with alpha radiation and its use in helping formulate the model of an atom containing a solid nucleus, Ernest Rutherford (1871–1937) had a crucial “surprising” observation. Some would say that this “mother of all surprising observations” led Rutherford directly to an abductive conjecture regarding a model for the atom that contained a solid dense nucleus surrounded by orbiting electrons. We gave the Google Gemini AI program the simple task of “write

about ernest rutherford and the tissue paper quote.” What follows is the first draft narrative that Gemini provided:

Ernest Rutherford, a pioneering nuclear physicist, famously used the analogy of “tissue paper” to describe his astonishment at the results of his gold-foil experiment. This experiment, conducted in 1909, revolutionized our understanding of the atom.

Prior to Rutherford’s work, the prevailing atomic model, the plum pudding model, envisioned the atom as a positively charged sphere with negatively charged electrons scattered throughout. Rutherford’s team fired alpha particles (positively charged nuclei of helium atoms) at a very thin sheet of gold foil. According to the plum pudding model, the alpha particles should have sailed straight through with minimal deflection.

However, to their surprise, some alpha particles bounced back at large angles, as if they had struck a massive, positively charged core. This result was akin to, as Rutherford himself said, “firing a 15-inch shell at a piece of tissue paper and it came back and hit you.” The deflection implied the existence of a tiny, incredibly dense center within the atom, which Rutherford later named the nucleus.

This discovery shattered the plum pudding model and paved the way for the nuclear model of the atom, where most of the mass and positive charge is concentrated in the nucleus, with electrons orbiting around it. Rutherford’s “tissue paper” quote perfectly captures the sheer unexpectedness and significance of his findings, which fundamentally changed our view of the microscopic world.

There are many biographies written about Ernest Rutherford and his importance as “the father of nuclear physics.” One of the more recent and concisely written is by Richard Reeves (2008), *A Force of Nature, the Frontier Genius of Ernest Rutherford* (W. W. Norton & Company, New York).