THERAPEUTIC, TINTING, AND TASTE-RELATED MOLECULES: OTHER FACETS OF SERENDIPITY

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Abstract. Serendipity has undeniably become an intrinsic factor in performing research. It may knock, pop up or ring at any moment, and the scientist is ready to hear it and to pounce on a surprise. While experimenting, the researcher in chemistry wishes the serendipity will manifest, bringing about an unmet novelty. Fortuitous findings have provided the human society a wide range of valuable chemical items with prominent properties. Therapeutic compounds such as quinine, penicillin, aspirin, and insulin, whose properties were come across, retain their unshakable supremacy within the human community. Prussian blue and most leading dyes such as mauveine, alizarin, indigo, and phthalocyanine were merely the results of accident. Some taste-related molecules, sweet and bitter ones, were the products of unplanned projects. Our today's world civilization is partly indebted to the serendipity and its propitious occurrence.

Keywords: serendipity in research, medicines, dyes, taste-related molecules

"*Accidental discoveries are common, one might say almost the rule, in chemistry but rare in mechanical engineering. It is much more likely that a chemist would fortuitously turn up some new and surprising property in a known compound than that an engineer would group together pieces of metal with one idea in mind and discover he had stumbled across a device that he had not been seeking.*"

John Jewkes, David Sawers, Richard Stillerman (economists), 1958.

Without the advent of science and technology, our world would probably be different from what it stands today. But, in turn, what would science and technology have been like if the serendipity service was out of order? Fortunately, and for the welfare of mankind, it surreptitiously sneaks in and manifests at any propitious moment providing the right move. An Arabic proverb states "*Blessing is merited for those who move (work).*" Thus, the serendipity happens only to those who work towards their objectives. In this line, the Louis Pasteur's thought is felt still up-to-date: "*In the fields of observation, chance favors only those minds that have been prepared*". Important is to recall, but non-exhaustively, that the serendipity has made many landmarks in science. The fortuitous discovery of X-rays by Wilhelm Conrad Röntgen (1845-1923) has entailed many of its uses: medical centers, identification of elements and their isotopes, crystallography (structures of polypeptides, vitamin B_{12}). The unexpected result of a mixture of left-handed and right-handed sodium ammonium tartrates by Louis Pasteur (1822-1895), has led to the asymmetric synthesis in organic chemistry. Free radical reactions would not have been deciphered if Moses Gomberg (1866-1947) did not observe the persistent yellow solution of the system Ph_3CCl/Ag. The world enjoys the various uses of polyethylene, a very widespread and reputed plastic, and the credit goes to its haphazard finding by E. W. Fawcett and R. O. Gibson. Serendipity did more: Teflon, a unique plastic with unmet properties, was discovered by Roy Joseph Plunkett (1910-1994) and Jack Rebock while working on new freons. It was the gracefulness of serendipity that made George de Mesteral (1907-1990) take a walk in the woods by a Summer day to have the cockleburs clung to his clothes, which engaged him in the design of Velcro. Some Nobel Prize laureates are indebted to serendipity that worked at the right for them: Sir Harry W. Kroto (b.1939), Richard E. Smalley (b.1943), and Robert F. Curl (b.1923) for fullerene C_{60} discovery; Hideko Shirakawa (b.1936) for his conducting polyacetylene discovery; Roald Hoffmann (b.1937) and Robert Burns Woodward (1917-1979) for establishment of the serendipity-inducing "*Woodward-Hoffmann rules*"; and Karl Ziegler (1898-1973) and Giulio Natta (1903-1979) for their stereoregular polymerization.

Serendipity widened its occurrence to other fields of research. One of its attractive issues resides in the fields of the medicinal substances, the coloring compounds and the tasting molecules. In this paper, the accidental findings of the healing, dyeing, and tasting properties of some molecules are outlined.

THERAPEUTIC MOLECULES

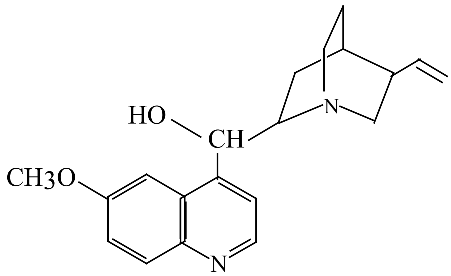
"*Nearly all the great discoveries in chemotherapy have been made as a result of a false hypothesis or due to a so-called observation*"

Alexander Kohn (microbiologist), 1989.

Quinine (1639)

For a sick person, alleviating his pain by eating, tasting, smelling, or touching a naturally occurring substance from an existing matter such as a tree, water, or air, is very serendipitous.

The anti-malarial activity of quinine has been credited to a *serendipitous legend* starring an Indian from South America who was suffering from Malaria. Once, this Indian was in a jungle high in the Andes, he desperately wanted to quench his thirst and found around only a small and bitter-tasting pool of water. He *unwittingly* ingested the quinine from this water because this pool was nearby a type of tree called *cinchona* whose bark was thought to be poisonous.



Quinine

Miraculously, the Indian's fever ceased afterwards and he quickly and blissfully brought the news to his community. From then, the bark known as *quina-quina* (meaning 'bark of barks' in native Indian tongue) by this tribe had been used from treating this disease. From then down this day the quinine-based medication has been an effective treatment for malaria-related complications. For the well-being of mankind, the serendipity reversed the fear of an awful poison into a benediction!

The use of cinchona bark was introduced in Europe in 1639 after the wonderful success in treating the Countess de Chinchón from a tertian fever, the wife of Spanish Viceroy of Peru. The prepared bark powder has been coined since then the "*Countess's powder*". To recall, this bark contains more than twenty-five alkaloids including quinine, which was extracted and separated in 1820 by the French chemists, Pierre Joseph Pelletier (1786-1846) and Joseph Bienaimé Caventou (1795-1877). In 1852, Louis Pasteur undertook the first stereochemical investigation, identifying quinine as a *levo-rotatory* substance. In 1854, Adolph Strecker (1822-1871) established the quinine formula as $C_{20}H_{24}N_2O_2$, which was later confirmed by Zdenko Hans Skraup (1887-1906). However, the correct atom connection in the quinine molecule was set mostly by Paul Rabe (1869-1952) in 1907. Because of the existing four chiral carbon centers meaning 16 stereoisomers, its synthesis has been a real challenge. In fact, it took more than hundred years to finally come up with the real quinine molecule. Nonetheless, it is worth citing some of the many organic synthetic chemists who have been well delved into the synthesis of quinine throughout the many years: August Wilhelm Hoffmann (1818-1892), Sir Williams Henry Perkin (1838-1907), Paul Rabe, Vladimir Prelog (1906-1998), Robert Burns Woodward, William von Eggers Doering (b.1917), Milan R. Uskokovic, Marshal Demotte Gates (1915-2003), and Gilbert Stork (b.1921). The first synthesis of quinine in 1944 by Woodward and Doering was partial, nonetheless that success made a front-page news in the world. It was only in 2001 that Stork successfully reached the total synthesis of quinine in its real shape. Aside from the Stork results, the real compounds found by other workers actually lacked stereochemical control, and all their synthetic routes (including Stork's) required no less than 13 steps. Unfortunately, the yields did not exceed 7%. In 2004, two laboratories headed by Eric N. Jacobsen and Y. Kobayashi reported the catalytic and stereocontrolled syntheses of quinine.

What makes quinine a valuable item sought for is the fact that Malaria remains the major disease affecting nearly 40% of the world's population; according to the 2000 report of the World Health Organization, malaria killed about 1.5 to 2.7 million lives, mostly children.

Vaccine (1796)

Probably, no action better than vaccination had been so effective in preventing diseases and, thus saving lives. A quite daring action was the direct experimentation on humans, which had been a common practice in 18th century. Vaccination was the first example known of this practice and therefore was discovered serendipitously. In 1796, the British surgeon, Edward Jenner (1749-1823) had been told, when he was a 19-year old medical student, by a dairymaid that people who caught the cowpox (a harmless disease caught via a contact with cows) never got smallpox. Similarly to Gregor Mendel and his heredity law development, had Jenner been lived in a different place or in a different time, he would have missed these observations. After being fermented in his mind for thirty years, he took it seriously and started to perform the experiment on James Phipps, an eight-year-old boy; he took samples from the cowpox sores, which had been developed on the hands of a young milkmaid Sarah Nelmes and inoculated the pus extracted from the sores on the young boy. This latter felt a slight fever and developed only a few lesions. Some months later, Jenner inoculated an extract containing the smallpox to see the ultimate effect. Surprisingly, the boy remained unscathed and no disease had appeared. This stunning result had led to the vaccination, which has been practiced up until now, and through which many contagious diseases have been disappeared in some countries of the world, such as tuberculosis.

As smallpox was a terrifying disease, Jenner became a worldwide celebrity. For many years the anniversary of the vaccination of the boy Phipps was celebrated as a holiday in Germany. Napoleon released two English Prisoners of War on being told that Jenner had personally asked for their release; Napoleon said as to Jenner: "*Ah, we can refuse nothing to that name*."

Albeit its discovery was credited to Jenner, the vaccination has been mostly and tightly linked to Louis Pasteur. Indeed, Louis Pasteur reaped its benefits in making tremendous accomplishments in the vaccination. In the 1880s, he developed vaccines against hydrophobia, rabies, chicken cholera, and anthrax. It is worthy to recall that Pasteur experienced health difficulties that, probably, impelled him to work for that purpose; three of his five children died at an early age, and he got many stroke brains that made him partly paralyzed. The immunization is always practiced as an alternative and effective way to look for in order to combat a malady. A Louis Pasteur's great accomplishment lies in the fact that mankind is made happier for being fearless of diseases.

The word "vaccination" was the term chosen by Pasteur instead of "inoculation" of Jenner. Vaccination consists of injecting a microbe into a person or animal's body in order to develop immunity against this microbe itself, and therefore, to avoid developing the illness that may be caused by this microbe.

Insulin (1889)

Not only had the chance brought about the artificial sweeteners (as developed below) for the benefit to diabetics but also it had revealed that the lack of a substance known as "insulin" causes this illness. The insulin is in fact a hormone secreted by pancreas that regulates the glucose metabolism. Based on recent estimates, insulin saves more than 15 million diabetes living today, and all scientists involved in the uncovering of the vital role of this substance are humbly saluted.

In 1889, two German doctors, Joseph von Mering (1849-1908) and Oscar Minkowski (1858-1931) took out the pancreas from a healthy dog to understand the role of this organ in the digestion. Some days later, they noticed a swarm of flies around the dog's urine, feeding from it. Fortunately, the place of that surgery was not immediately cleaned from urine. Curious of what they saw happening, they analyzed the urine to find out what really attracted these flies, a kind of chemotaxis. They found that on removing its pancreas, the dog was secreting sugar in its urine, a symptom of diabetes. As the experimenting dog stood healthy before the operation, they firmly concluded that there is a tight link between the pancreas and the diabetes. Their further study revealed the existence of a molecule secreted and released by the pancreas, a molecule that equilibrates the sugar in the body.

However, insulin is best known through John J. R. MacLeod (1876-1935) and Frederick G. Banting (1891-1941), the two Canadian scientists. The story began in October 1920 with the Canadian surgeon Banting. He could not sleep the night before October 30, 1920, and as the French proverb dictates "*Night provides advices*" (La nuit donne des conseils), he ruminated over an article he read on the link between the Islets of Langerhans (clusters of cells within the pancreas) and diabetes.[1)] Like Alfred Nobel and his last-night conceived idea about a safer nitroglycerin, he woke late that night and sketched the following steps:

Diabetus

Ligate pancreatic ducts of dogs

Keep dog alive till acini degenerate leaving Islets
Try to insolate the internal secretion of these to relieve glycosurea.

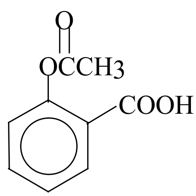
On May 17, 1921, Banting started working on this project at MacLeod's laboratory (MacLeod was a professor of physiology at the University of Toronto at that time) assisted by Charles H. Best (1899-1978). Their work consisted basically on performing pancreatectomies on dogs and extracted insulin. In December of 1921, they were able to extract it by using alcohol but in an impure form. The fate was that Dr. J. Bertram Collip (1892-1965), a professor at the University of Alberta, was on Sabbatical year at the University of Toronto. He joined the group and was assigned the purification task of the extracted insulin. Collip succeeded in purifying it in summer 1921.

On January 23, 1922, the first test was performed on Leonard Thompson, a 14-year-old boy, who was desperately sick. The result was astonishingly marvelous, the boy improved in a few hours.

No later than the ensuing year, 1923, Banting and MacLeod received the Nobel Prize in medicine and brought the first such a prize to Canada.[2)] On the other hand, Frederick Sanger (b.1918) in 1953 was able to determine the amino acid sequence of bovine insulin. He found that the latter substance consisted of 51 amino acid residues in two peptide chains, called the A and B chains. Frederick Sanger was twice a Nobel Prize recipient, in 1958 for his contribution on insulin structure and in 1980 for his work on nucleic acids.

Aspirin (1897)

One of the miraculous drugs that have been beneficial to humanity is aspirin. Its discovery remains an important accomplishment in medical science. The start was just serendipitous. In ancient times (2,000 years before the aspirin discovery), Hippocrates (460-377 B.C. in Greece), the Father of modern medicine, used a bitter white powder from the bark of a willow tree for medical treatments, headache and pain relief.



Aspirin

This powder, which is now known as salicin, was able to relieve childbirth pain and to alleviate fever. Amazingly, it was until 1820s that the isolation of salicin, the active matter of this white powder, was performed.[3] It was found that salicin is chemically a glucoside which upon hydrolysis afforded saligenin (*o*-hydroxybenzyl alcohol). Salicin is a pharmacological ancestor of drugs called "salicylates", the best of which is the most widely used drug, aspirin.

In 1853, the French chemist Charles Frédéric Gerhardt (1816-1856) attempted the reaction of sodium salicylate salt with acetyl chloride and came up with acetyl-salicylic acid in an impure, thus unstable, form. Gerhardt abandoned this process because he thought it was too tedious. The fate was to wait for about forty-four years to revive the Gerhardt's process. Indeed, in 1897, Felix Hoffmann (1868-1946) resuscitated this process, trying to come up with a drug that relieved his father's arthritis pain.[4] At the start, Hoffmann was searching for an alternative to sodium salicylate that had been used for such an illness at the time, because this medication implied severe stomach irritation after its administration. On August 10, 1897, his work was crowned with success in making the wonder drug, the acetylsalicylic acid (ASA) in a pure and stable form. This product miraculously alleviated his father's pain without stomach irritation.

Noting the tremendous ailment relieving ability of this chemical, Hoffmann who was working at Bayer Company, strongly recommended his company to start manufacturing it. Bayer staff did not agree with him, arguing that ASA would weaken the heart at higher doses of salicylates. Aspirin was patented on March 6, 1899.[5]

Also taken for serendipitous is the fact that scientists, to their utter delight, realized that the curing potency of a drug is not confined to one kind of disease but to some others. It is actually the case of aspirin. Aspirin, an over-the counter drug (OTC), has been used against many ailments including gout, tonsilitis, pleurisy, headaches, fever, and inflammation. Best of all, it is prescribed for cardiovascular disease and prevention of cancer and heart attack. Isn't it a blessing that aspirin may save as many as 10,000 lives who suffer from heart disease? In 2003, reports have shown that Americans have taken up yearly about 80 billion aspirin tablets and, within the last century, about trillion aspirin tablets have been consumed worldwide.

Chlorethazine (1918)

While there is a general disagreement that the war is not, by no means, profitable for mankind, an exception is that of the World War I (WWI) in which the mustard gas had been employed as a chemical warfare.

$$Cl\text{-}CH_2CH_2 - S - CH_2CH_2\text{-}Cl$$

Chlorethazine

It is fitting to quote the French proverb: "*Le malheur des uns fait le bonheur des autres*." (*The misfortune of some people makes the happiness of others*). Indeed, that is the case of mustard gas. This substance, the bis-β-chloroethyl sulfide, is characterized by : 1) a high boiling liquid (boiling point of 217.5 °C), not a gas, that can be dispersed as mist of tiny droplets, 2) a mustard-like odor, and 3) a blistering effect (a powerful vesicant agent). A concentration of only 0.15 mg/L of mustard gas is lethal in ten minutes and severe conjunctivitis can be engendered by only 0.001 mg/L after one-hour exposure. The physicians in charge of the World War victims diagnosed a lack of white globules. This valuable remark has been related to the effect of the mustard gas and was the impetus to the development of chlorethazine whose structure is akin to that of mustard gas; the chlorethazine has been employed in chemotherapy and the cure for some lymphomas.

Lysozyme, Penicillin (1922, 1928)

The *fortuitous* discovery of lysozyme, an enzyme made of 129 aminoacid residues, is a fascinating story. The lucky man was **Alexander Fleming** (1881-1955), the pioneer bacteriologist at St. Mary's Hospital in London. A much-shortened version of this story is quoted in the organic book of Graham Solomons:

> *[O]ne day in 1922 Alexander Fleming was suffering from a cold. This is not unusual in London, but Fleming was a most unusual man and he took advantage of the cold in a characteristic way. He allowed a few drops of his nasal mucus to fall on a culture of bacteria he was working with and then put the plate to one side to see what would happen. Imagine his excitement when he discovered some time later that the bacteria near the mucus had dissolved away. For a while he thought his ambition of finding a universal antibiotic had been realized. In a burst of activity he quickly established that the antibacterial action of the mucus was due to the presence of an enzyme; he called this substance lysozyme because of the capacity to lyse, or dissolve the bacterial cells. Lysozyme was soon discovered in many tissues and secretions of the human body, in plants and most plentifully of all in the white of an egg. Unfortunately Fleming found that it is not effective against the most harmful bacteria. He had to wait seven years before a strangely similar experiment revealed the existence of a genuinely effective antibiotic: penicillin.*

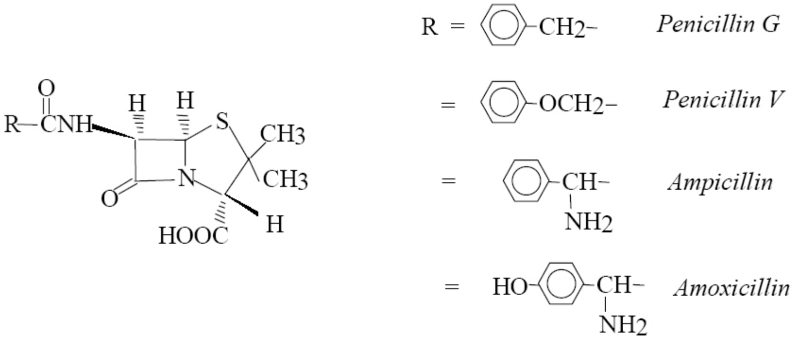
It is also recounted that he allowed the drops of his tears, instead of his nasal mucus, to fall on the bacteria culture.

It is quite impressive to realize that the events of some discoveries are knotted in a fateful fashion. As just stated in the above quotation, the discovery of penicillin, the first synthetic antibiotic, followed the same path as that of lysozyme. After he served as doctor in the battlefield in the WWI, Fleming came back to St. Mary to devote himself to find out an effective antiseptic for the simple infections of which the wounded warriors died. In 1928, he worked on the cultures of microorganisms such as « *Staphylococcus aureus* ».[6) He used to open every day his Petri dishes containing the cultures to examine them under the microscope. One day, he noticed a blue-greenish color of a mold contaminating the cultures. He stopped and said: "*That's funny*". Probably, other experimenters would have just discarded these contaminated products as they probably thought to be of no avail, but it was not the case as to Fleming, the keen-sighted researcher. He said:

> *[B]ut for the previous experience, I would have thrown the plate away, as many bacteriologists have done before.*

He looked closer at these products and examined carefully this phenomenon. He wittily noticed that the bacteria colonies distant from the mold area have been destroyed. He ingeniously deduced that the broth in which the molds have been germinated might have a potential inhibiting or deadly effect on the pathogenic organisms. This broth was later identified as *Penicillium notatum* and the term penicillin[7) was attributed to the antibacterial substance fermented by the broth. Penicillin was isolated by the Australian-English pathologist Howard Walter Florey (1898-1968) and the German-English biochemist Ernst Boris Chain (1906-1979) in 1941; its antibiotic activity was successfully demonstrated. In the mid-1940s, penicillin was widely used to treat infectious diseases such as pneumonia and rheumatic fever. By 1945, a half a ton of this antibiotic was produced by means of the mold culture process.

These haphazard discoveries put Alexander Fleming on the road to the Nobel Prize in medicine in 1945, shared with Howard Florey and Ernest Chain. The penicillin discovery has ushered other antibiotics in the era of the medicine such as tetracyclines and streptomycin.



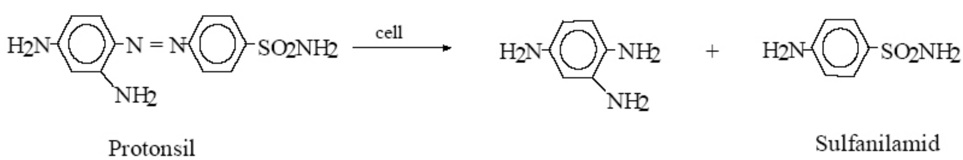
Penicillin

Sulfamides (1932)

What may spark one's curiosity is that the modern chemotherapy started with a number of dyes. In 1891, Paul Ehrlich (1854-1915, Nobel Prize in medicine in 1908) aimed at using methylene blue[8] in the treatment of nervous disorders and found that this dye could have a clinical effect in treating Malaria. Moreover, he discovered in 1907 the curative property of Trypan Red I (a dye) when tested for trypanosomiasis, a sleeping sickness.

Furthermore, it was found that bacteria can be stained with dyes in order to show up under microscopy. By means of this staining method, cholera and tuberculosis bacilli were discovered.

The discovery of the bacterial activity of the sulfanilamide remains an upheaval in the pharmacological field. *The chance* has brought forth the first sulfa drug. In 1932, Fritz Mietzsch (1896-1958) and Joseph Klarer (1898-1953), two chemists of Bayer Company, have prepared an azo dye called *Protonsil*. This dye was intended only to color some bacteria for an identification purpose in a multistep work. Its biological assay *in vitro* proved to be of no bacterial activity. In 1927, Bayer Company hired Gerhardt Domagk[9] (1895-1964), a German pathologist, to elucidate the chemotherapeutic activity of the sulfonamides to substitute for the arsenical compounds. In 1935, Domagk succeeded and showed its bactericide action *in vivo* by experimenting it on infected mice. In those days, *the chance* has made things proceed *incidentally* with the illness of Domagk's daughter who was affected with a streptococcal infection from a pin-prick. A culminating and unique venture was that of Domagk when he decided to administer orally a dose of Protonsil to his dying daughter, as a last chance for a possible recovery.[10] The result was *unexpectedly miraculous*: the Domagk's daughter was rapidly relieved.



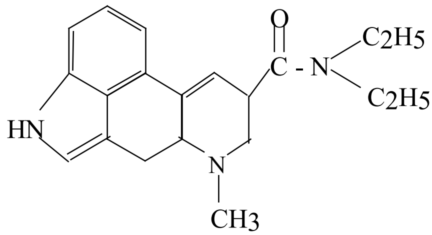
(1)

One year later, Ernest Fourneau (Pasteur Institute, France) elucidated the real mechanism of the Protonsil action on the cell: Protonsil molecule, in contact with cell, undergoes a fragmentation at the azo site yielding the active species, the sulfanilamide, Eq. (1). In 1939, Domagk was awarded with a Nobel Prize in medicine in honor to this epoch-making finding.

Bayer Company marketed its product as *Prontonsil red* and claimed its efficacy for streptococci, meningitus, and gonorrhea. A number of sulfa drugs have been spawned shortly after this discovery and their antibacterial activity has been ascertained; in 1964, more than 5000 sulfa drugs can be counted. Later, the Penicillin related antibiotics have partially substituted to sulfa drugs.

Lysergic acid diethylamide (LSD) (1943)

One of the most hallucinogenic molecules is lysergic acid diethylamide or lysergide, commonly abbreviated as LSD. The accidental discovery of its hallucinating property is a funny story. The daring readiness of its author to experiment this property on himself made the story a unique one.



LSD

This event resembled that of Domagk and his daughter. Albert Hoffmann (1907-1972), a Swiss chemist and a towering figure in alkaloid chemistry, inhaled minute amounts of the vapor that emanated from the flask containing LSD. Soon he started to become dizzy and drowsy. The story itself is well traced by him:

> *[I]n the afternoon of 16 April 1943…..I was seized by a peculiar sensation of vertigo and restlessness. Objects, as well as the shape of my associates in the laboratory, appeared to undergo optical changes. I was unable to concentrate on my work. In a dreamlike state I left for home, where an irresistible urge to lie down overcame me. I drew the curtains and immediately fell into a peculiar state similar to drunkenness, characterized by an exaggerated imagination with my eyes closed, fantastic pictures of extraordinary plasticity and intensive color seemed to surge toward me. After two hours this state gradually wore off.*

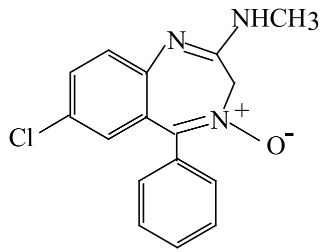
After experiencing these moments in an out-of-minded state, Hoffmann was amazed about what happened to him. To comprehend this unusual phenomenon, he courageously and deliberately took up orally about 0.25 mg of LSD tartrate, amount that is 2.5 – 12.5 times the dose required for hallucination (the amount that induces hallucination is in the range of 0.02 - 0.1 mg per person). He pursued describing this second event:

> *[A]fter 40 minutes, I noted the following symptoms in my laboratory journal: slight giddiness, restlessness, difficulty in concentration, visual disturbances, laughing….Later, I lost all count of time. I noticed with dismay that my environment was undergoing progressive changes.*

My visual field wavered and everything appeared deformed as in a faulty mirror. Space and time became more and more disorganized and I was overcome by a fear that I was going out of my mind. The worst part of it being that I was clearly aware of my condition. My power of observation was unimpaired.... Occasionally, I felt as if I were out of my body. I thought I had died. My ego seemed suspended somewhere in space, from where I saw my dead body lying on the sofa....It was particularly striking how acoustic perceptions, such as the noise of water gushing from a tap or the spoken word, were transformed into optical illusions. I then fell asleep and awakened the next morning somewhat tired but otherwise feeling perfectly well.

Benzodiazepines (1957)

The tranquilizing effect of some chemicals was found quite by *accident.* This concerns the benzodiazepine family (BDZ) that the chemist Leo H. Sternbach (1908-2005, Hoffman-Roche Laboratories, Nutely, New Jersey, USA) found their tranquilizing effect while conducting work on dyes, that is, the same path as with protonsil. He synthesized about 40 new six-membered ring compounds but all of them were pharmacologically inert. He finally treated one of these substances with methylamine and the resulting white crystalline product



Chlorodiazepoxide

was shelved for a later examination. The shelving lasted for about 18 months when a Sternbach's assistant found this product while he was clearing up the laboratory. *Fortunately*, the assistant did not throw it away but asked Sternbach who forgot it, whether to send it for screening. Sternbach thought a little while and decided to send it at Roche laboratories for examination. In July of 1957, Dr. Lowell Randall, the Roche laboratories director, sent to Sternbach a report of the clinical trial of the compound, writing the following:

[t]he substance has hypnotic, sedative, and antistrychnine effects in mice similar to meprobamate.

This substance was the chlorodiazepoxide or methaminodiazepoxide, a 1,4-benzodiazepine with a seven-membered ring structure. It was found that this drug was the most effective among the benzodiazepines and later marketed under the name "*Librium*". Two and a half years later, the benzodiazepines (diazepam, lorazepam…etc.) started to be commercialized. The arrival of these drugs into market has been viewed as a benediction, for the people have been suffering from the "*stress*" and the "*anxiety*" in the last two decades. On the contrary to the barbiturates, the benzodiazepines were claimed to be devoid of addiction-inducing effect.

Cis-Platins (1960)

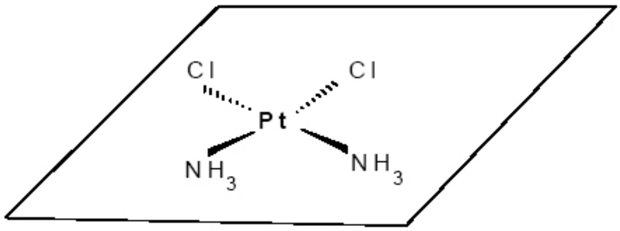
In 1845, Peyrone first prepared *cis*-$Pt(NH_3)_2Cl_2$ which came to be known as Peyrone's chloride. In 1893, Alfred Werner, the Father of coordination chemistry, elucidated its structure and discussed the *cis* and *trans* isomers. It took about 70 years before the *cis* isomer became a valuable compound.

In 1960, the biophysicist Barnett Rosenberg (b.1926) at Michigan State University launched a set of experiments in order to clarify the link between the mitosis phenomenon and the electric field of a dipole, that is, to show the interference of the electric field with the division of cultured bacterial cells. His initial curiosity stemmed from the similarity between the movement of the cells as they divided and multiplied and the movement of iron filings as they are scattered near a magnet. He keenly thought of a connection between the patterns of these two phenomena.

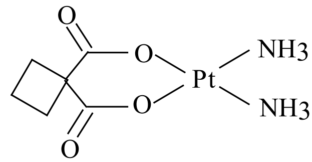
In order to avoid all interfering chemical reactions, the used electrodes were made out of platinum. In his first experiments, he noticed that the field generated between the platinum electrodes immersed into a solution containing *Escherichia Coli* seemed to prevent cell division and to induce filamentous cell growth; indeed, after turning on the current, he was surprised to see the bacteria growing in length but not dividing. The process of division started only after the electric current has been turned off. Rosenberg pondered on the interference of a possible electrochemical reaction with the cell division process. In his forthcoming work, he showed that these observed phenomena were not due to the electric field but to a platinum complex *casually* formed in the working medium. *The chance* has made things work against Rosenberg prudence, that is, his choice of platinum as an inert metal. Best of all, *the chance* has made the experiments be carried out in electrolytic media containing chloride ion (Cl^-) and ammonia (NH_3) which could have reacted with the tiny amount of platinum metal Pt(0) leached from the electrode. The platinum complex was *fortunately* the *cis*-$Pt(NH_3)_2Cl_2$ (*cis*DDP).

As the *cis*DPP effectively inhibited the cell division, Rosenberg foresaw its anti-cancer activity, that is, to prevent cancerous cell from dividing,

Of a particular significance, in 1972, the pharmacological trials of the *cis*-$Pt(NH_3)_2Cl_2$ were eminently promising, that is, a great anti-tumor activity was remarked. Since then, more than 11000 complexes of this type based on metals and metalloids have been prepared and tested in the inhibition of cell division by the National Cancer Institute (USA). In 1978, the complex *cis*-$Pt(NH_3)_2Cl_2$ ant its homologues (CHIP, CBDCA, JM-40, …etc.) were approved as an anti-tumorial drug by FDA (Food and Drug Administration) under the name "*CisPlatins*". Their anti-tumorial activity was demonstrated to be more pronounced particularly for ovarian and testicular carcinomas.



_Cis_Platin (_Cis_DPP)



Carboplatin

Clinical studies of the complexes of this kind revealed that the anti-tumorial activity is bound by stringent requirements in respect with the complex. To be effective, the complex should fulfill the following conditions: a) the oxidation state of Pt must be (II), b) aA square planar geometry of the complex, c) A *cis* geometry of two ligating nitrogens, each should have, at least, one hydrogen atom (*n*, *iso*, acyclic, heterocyclic amines), and d) The presence of good leaving groups such as Cl^-, Br^-, oxyanions, and carboxyxlates.

The explanation of the therapeutic inactivity of the *trans* isomer is still a matter of curiosity and remains unveiled. *Fortunately*, the isomer formed in the Rosenberg's experiments was the *cis*-$Pt(NH_3)_2Cl_2$, otherwise the cancer chemotherapy would have known a delay. Because the CisPlatins cause some side effects, Rosenberg made in 1985 a cognate compound, the carboplatin which had fewer side effects.

Artificial skin (1997)

A similar case to Domagk's with respect to his courageous decision is that of Dr. Frank J. Baker, an emergency medicine specialist at Chicago. In 1997, this doctor tested an artificial skin, a laboratory-made polymer, on insulin-dependent diabetics whose body tissue had been decomposed and complicated by a high blood sugar. Frank Baker tested it on his own tissue as he has had diabetics for four decades and was about to loose one of his feet because of hard-to-heal skin ulcers. The trial result was a miracle because not only this artificial skin covered his wound but also released some substances that make the tissue to grow back much faster. Baker's foot was indeed saved.

Table 1 compiles some other therapeutic drugs of which pharmacological activities were serendipitously demonstrated.

Table 1: Some serendipitous discoveries in drug research[11)]

Compound	Accidental Discovery
Acetanilide	Tested as internal antiseptic (instead of naphthalene)
Acetylsalicylic acid	Irreversible enzyme inhibitor (*vs.* salicylic acid)
Aminoglutethimide	Breast cancer treatment (instead of antiepileptic)
Amphetamine	Stimulant (instead of nasal decongestant)
Chloral hydrate	Prodrug of trichloroethanol (instead of chloroform)
Chlorodiazepoxide	Tranquilizer (unexpected chemical rearrangement)
Chloropromazine	Neuroleptic (tested to prevent surgical shock)
Cinnarizine	Cardiovascular (predominant to antihistaminic) activity
Cisplatin	cytotoxic effect of electrolysis product
Clonidine	antihypertensive (instead of nasal decongestant)
Cromoglycate	antiallergic (accidental formation of chromone dimer)
Cyclosporin	immunosuppressant (instead of antifugal agent)
Dichloroisoprenaline	в-blockade (instead of bronchodilation)
Dicoumarol	fatal cattle poisoning (bleeding) by moldy hay
Diethylstilbestrol	estrogenic impurity of anol (dimerization product)
Diphenyhydramine	allergy treatment caused prevention of travel sickness
Diphenoxylate	antidiarrhoic (instead of analgesic)
Disulfiram	hypersensitivity to alcohol
Ether	anesthetic activity in inhalation party
Etomidate	anesthetic (instead of chemotherapeutic) activity
Griseofulvin	growth inhibition of conifers on certain soils
Guanethidine	antihypertensive (instead of antitrypanosomal drug)
Haloperidol	neuroleptic (instead of analgetic) activity
Heparin	deterioration of lipid coagulant unmasked anticoagulant
Imipramine	antidepressant (instead of neuroleptic) activity
Iproniazid	antidepressant (instead of tuberculostatic) activity
Isoniazid	tuberculostatic activity of organic intermediate
Levamisole	immunomodulating (instead of antiparasitic) agent
Lithium carbonate	antidepressant activity of lithium urate
Lysergide (LSD)	hallucinogenic (instead of cardiovascular) activity
Meprobamate	tranquilizer (instead of muscle relaxant)
Merbaphen	diuretic activity (of antisyphilitic agent)
Methaqualone	hypnotic (instead of antimalarial activity)
Mifepristone	antiprogesterone (instead of glucocorticoid) activity
Naftifine	antifungal rearrangement product of CNS drug
Nalorphine	antagonism (instead of respiratory stimulation)
Nitrogen mustard	cytotoxicity observed after ship bombardment
Nitroglycerin	antianginal activity (headache after inhalation)
Nitrous oxide	accidental wounding in laughing gas session
Norethynodrel/Mestranol	estrogenic impurity in the first oral contraceptive
Penicillin	antibiotic activity of Penicillium infection
Pethidine (meperidine)	morphine agonist (instead of spasmolydic)
Phenylbutazone	antiinflammatory activity of solubility enhancer

Phenolphthalein	laxative (tested as label for cheap wines)
Praziquantel	antiparasitic agent (instead of antidepressant activity)
Prednisone	bacterial oxidation produced highly active analog
Propafenone	antiarrhthmic (instead of в-blocker)
Sulphamidochrysoidine	prodrug of sulfanilamide (active only in vivo)12)
Sulfonamides, various	diuretic and antidiabetic side effects
Tamoxifen	antiestrogenic activity cis-isomer
Urethane	hypnotic activity (instead of alcohol prodrug)
Valproic acid	anticonvulsant (solubility enhancer for various drugs)
Warfarin	low acute toxicity of rat poison in attempted suicide

TINTING MOLECULES

"*Nothing is perhaps more peculiar than the process by which one obtains Prussian blue, and it must be owned that, if chance had not taken a hand, a profound theory would be necessary to invent it*".

Jean Hellot (chemist), 1762.

Prussian blue (1704)

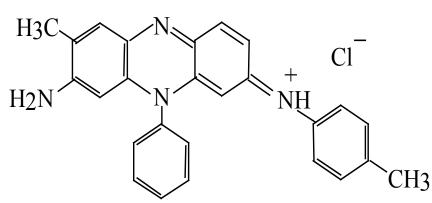
The first modern synthetic pigment was *inadvertently* created by the Prussian (Germany) Heinrich Diesbach in 1704. He attempted to make the cochineal red lake by heating the dried blood successively with the potash (potassium carbonate) and the green vitriol (iron sulfate). To recall, colormen were used to prepare the crimson red pigment by crushing the cochineal insects with potash and vitriol (the term "Lake" was used for any dye-based pigment).The fate was the use of a cheaper potash, that is the animal oil-contaminated potash provided by his friend, Johann Konrad Dippel. Diesbach realized that the cheap potash turned down his economical plan because the product he obtained was extremely pale and not the expected red. But, to his surprise, upon concentrating the product, it turned purple before becoming deep blue. Lacking knowledge in chemistry, he asked Dippel for an explanation for what he saw, the latter pointed only to a plausible chemical reaction between the vitriol and the contaminated potash. The product was actually the result of the two sequential reactions: the reaction of the animal oil (from blood) with potassium carbonate to give the potassium ferrocyanide; the latter, on mixing with iron sulfate yields iron ferrocyanide, $Fe_4[Fe(CN)_6]_3$, the Prussian blue.

By now, the inorganic chemists can easily make it by treating a solution of Fe(III) with hexacyanoferrate (II). However, they may obtain the *Turnbull's blue* when treating Fe(II) with hexacyanoferrate(III). Diesbach gave the name "*Prussian blue"* to his new and unexpected substance because he was Prussian. This substance has been known under other names: Berlin blue, Antwerp blue, Chinese blue, Paris blue. It was viewed as being "*equal to or excelling ultramarine*" and widely used as the blue pigment in paint formulations in Europe the 18th century.

Mauveine (1856)

Sir Williams Henry Perkin (1838-1907), an eminent young English chemist, is considered the forerunner of the synthetic dyes. While working under the German chemist August Wilhelm Hofmann (1818-1892) supervision, he had conducted some organic syntheses of his own conception and for his own curiosity. At the age of seventeen, he audaciously undertook the synthesis of the epoch molecule, the quinine, a miraculous drug for the devastating Malaria. Perkin has learned the Hofmann's interest in making this coal tar. Had Hofmann or Perkin known of the complex structure of the quinine molecule, they would not have thought of trying to make it. Their ignorance had fatefully led to the unexpected dye. For this purpose, in 1856 while on his Easter vacation he attempted the oxidation of allyltoluidine from coal-tar with the potassium dichromate; he was about to discard the messy mixture he obtained, but he noticed with surprise a reddish brown precipitate which turned out to a beautiful purple upon adding methanol to it. This observation compelled him to remake the experiment with crude aniline (contaminated with allyltoluidine); he isolated, besides a black precipitate, a purple and brilliant substance in about 5%. Unlike others who came across this beautiful and bright substance before him, he foresighted the commercial usefulness of his discovery. With eagerness, he sent this purple material to the Scottish dyers John Pullar & Sons in Perth to perform the necessary dyeing quality tests. These dyers were impressed by the results saying: "*Your discovery does not make the goods expensive*". The color and fastness tests have been shown to be promising and, these results were the swivel point of the Perkin career. Indeed, he dropped his scientific career as a prominent and talented chemist, and devoted himself to the industrial manufacture of this new synthetic dye which was named *Mauve* or *Mauveine* by French dyers. In 1862, Queen Victoria made an appearance in a silk gown dyed with mauveine.

In 1994 (138 years after the mauveine discovery!), Meth-Cohn and Smith reported that the analysis of an original sample of mauveine by TLC, NMR and MS



Mauveine

methods has shown the existence of two major products, instead of one. Had Perkin employed pure aniline instead of the crude one available then, mauveine would have not been obtained. It was therefore the *adventitious* toluidine contamination that provided us one of the most known dye.

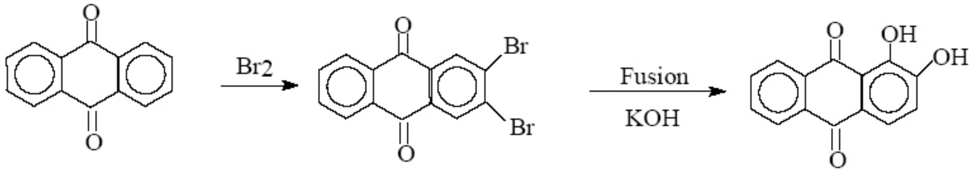
Perkin discovered anthraquinone while nitrating anthracene but did not resume working with this compound.

Alizarin (1868)

Both natural alizarin and indigo were dyestuffs of a paramount importance in the Middle Ages, and consequently, people were always interested in them. They were used to coloring the Egyptian mummy clothes. In 1820, two French chemists, Colin and Robiquet, isolated a red compound from the madder root, which they called it "*alizarine*" after the Levantine word for madder: *alzari*. In 1868 Karl Graebe (1841-1927) and Karl Theodor Libermann (1842-1914), while working under Adolpf Baeyer's supervision, succeeded in making alizarin by means of the reaction shown in Eq. (2). Because the natural alizarin was known to bear quinone frame, Graebe of the Bayer Company, before embarking on this reaction, first ascertained that quinones are actually cyclic compounds as suggested by Friedrich August Kekulé at that time. We shall salute the audacity of these two chemists to try to make this substance without knowing its real structure and not to be entirely sure to obtain it; yet, chloranil, a quinoid molecule, served for them as a model. They started by brominating anthraquinone followed by the fusion of the obtained product with potassium hydroxide. They remarked the great resemblance between the synthesized product and the natural alizarin. This work was later known to be distinguished by two features: 1) the formation of only one isomer among others, 2) a peculiar rearrangement which might have occurred in the fusion step, that is, a possible opening of the quinone form followed by a closure in an opposite direction.

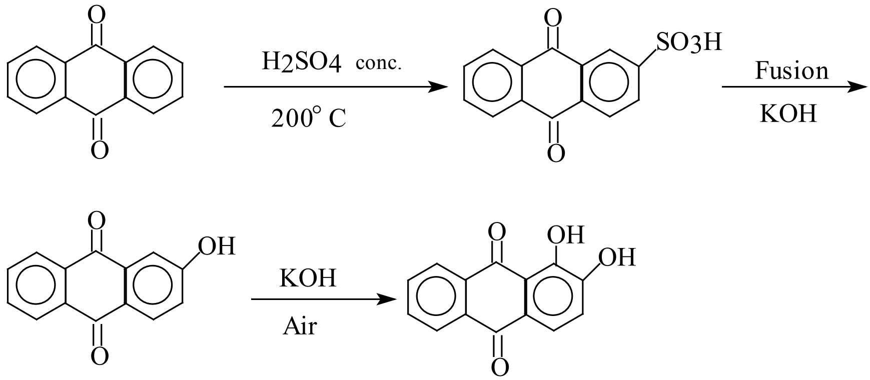
Due the high cost of the bromine coupled with a problem of the fusion process, this reaction was not conceived as an industrial procedure of making this dye. Inspired, however, from the findings of Kékulé, Wurtz, and Dusart on the hydroxylation of phenolic compounds which took place at a low temperature via a sulfonation process, Graebe and Liebermann applied these conditions to the anthraquinone to introduce an OH group. Unfortunately, they noticed that the anthraquinone withstood the sulfonation at these conditions, thus their attempt failed.

It was the *inadvertent* observation of the BASF's chief chemist, Heinrich Caro (well known by his acid, H_2SO_5), of a water-soluble sulfur-containing substance obtained from a reaction of anthraquinone with concentrated sulfuric acid at an elevated temperature, 200°C, Eq. (3). It is reported that Caro has also contributed to the synthesis of Alizarin and other organic substances. This accidental discovery solved the standing problem of Graebe and Liebermann. In fact, the industrial production of alizarin in Germany jumped from 40 tons in 1870 to 9500 tons in 1879.



(2)

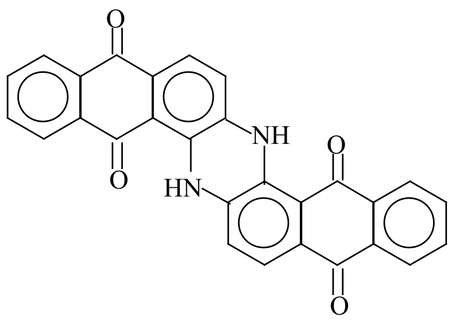
Alizarin



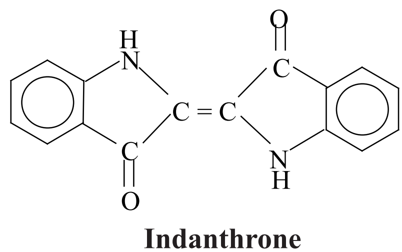
(3)

Indigo, **Indanthrone** (1901)

Indigo, another prominent dye, is also featured by its accidental fate. In the19th century the natural extract of indigo came out of India; in 1870, there were 2800 indigo factories in this country. Even though efforts of Adolf Baeyer and Heinrich Caro had been devoted to



Indigo



Indanthrone

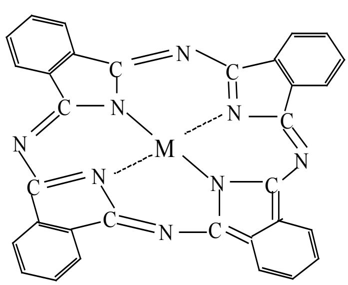
make the synthetic indigo, it was the accidental fate that cracked the nut. It is told that a chemist named Sapper while he was heating some organic chemicals (coal tar), incidentally broke his thermometer and the mercury dipped into the organic mixture. Being a widely awake chemist, he noticed a difference in the reaction with the intended one. His further work suggested to him that phthalic anhydride has been formed which could be readily transformed into indigo; the mercury would have served as a catalyst in the oxidation of the naphthalene, one coal tar component, into the unexpected but valuable phthalic anhydride. Yet, the synthesis developed by Karl Heumann at the Swiss Federal Polytechnic in Zürich starting with naphtalene, which at that time was a waste product of the coal-tar industry, has been a leading industrial procedure of indigo with some modifications.

One of the Heumann's students, René Bohn, has been conducting an active research on the synthesis of anthraquinone-based dyes. In 1901, he conceived to produce a parent indigo, a vat dye, starting with anthraquinone following the steps of the Heumann's indigo synthesis. While the first step seemed to be straightforward, the condensation of β-aminoanthraquinone with chloroacetic acid, the ring closure step required drastic conditions because the substitution reaction on anthraquinone is known to be difficult and necessitates higher temperatures. This ring closure was easily promoted by the fusion with caustic alkali in the Heumann's indigo synthesis. Yet, with drastic conditions, Bohn could obtain a blue substance but its structure proved to be the one shown above, and not the expected one (like the indigo). This substance is now commonly known as indanthrone and can be synthesized via other routes.

Phthalocynanines (1927)

The story of the phthalocyanine is a triple-faced one. It started with Braun and Tchermic who tried in 1907 the synthesis of *o*-cyanobenzamide by dehydrating phthalalamide using acetic anhydride. Instead of the desired product, they found a small amount of a bright bluish substance. Unfortunately, these workers did not substantiate the significance of their discovery.

In 1927, the Swiss chemists H. de Diesbach and E. von der Weid observed the formation of a deep blue pigment when attempting to prepare *o*-phthalonitrile, by heating a pyridine solution of *o*-dibromobenzene at 200°C in the presence of cuprous cyanide.



(M = Cu, Fe,....)

Phthalocyanine

Unfortunately, this beautifully colored substance was, carelessly, not characterized.

In the ensuing year, the chemists of Scottish Dyes at Grangemouth (A. G. Dandridge, Edinburgh, Great Britain) noticed that their phthalimide produced by the reaction of phthalic anhydride with ammonia in an open vessel, was contaminated with a dark blue iron-containing pigment. What made this finding an *accidental* one was that the glass-made inner wall of the doubly-jacketed reactor *adventitiously* shattered during the reaction. This cracking has allowed the reaction mixture to be exposed to the steel-made outer wall of the reactor, and the unexpected substance was thus produced. The Scottish chemists positively guessed what has occurred and promptly replicated the conditions at the laboratory scale. They successfully obtained the unwanted impurity, the iron phthalocyanine, by reacting phthalic anhydride with ammonia in the presence of iron filings. In 1929, the Scottish Dyes Company obtained a patent for the preparation of this substance. It was Sir Reginald Patrick Linstead of Imperial College of London who coined the name "*phthalocycanine"* (phthalo meaning oil; cyanine meaning blue) to this colored compound, and in 1934 they disclosed its macro-structure. Later, M. Robertson showed by X-ray analysis that the structure of this molecule is planar, rather than the three-dimensional one.

The first commercialized phthalocyanine by ICI firm was the copper phthalocyanine in 1935, under the trade name "*Monastral B*", a preeminent blue. The phthalocyanines are widely employed as pigments in many industries: automotive coatings, lacquers, plastics, printing inks, dyeing matter for cellulose viscose and acetate fibers (*Blue Indanthrene 4G*). It is claimed that it is the best blue pigment for three-color printing. A distinguished property of the phthalocyanines is their tendency to sublime into beautifully large crystals. The first organic compound analyzed by X-ray diffraction was a phthalocyanine for structure elucidation. Over the past decade, the modified phthalocyanines have been making big inroads into the "*Hi Tech*" devices such electronics, optoelectronics, optical data recording, non linear optics NLO. The polymer-supported phthalocycanines are being used as electrocatalysts.

C.J.T. Cronshaw, overwhelmed with astonishment with regard to the phthalocyanine molecule, wrote:

> *[A]lthough the existence of the phthalocyanines* ***was not predicted****, and was perhaps* ***not even predictable****, yet now the discovery has been made and the structure of the molecule ascertained, no one can fail to remark the inevitability of the compound. Its right of existence is almost declamatory! It is remarkable how readily at the appropriate temperature of reaction, and in the presence of such a metal as copper, the four integral components almost snap into position.*

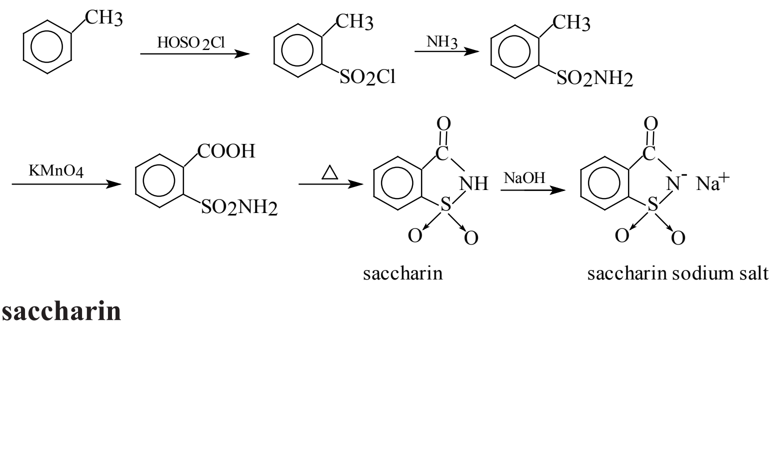
"*The sweet taste of aspartame could have not been predicted from a knowledge of the properties of the component amino acids – one of them has a 'flat' taste and the other is bitter. The extremely sweet taste that resulted from the combination of the two and conversion to the methyl ester was a complete surprise.*"

Royston M. Roberts (chemist), 1989.

Synthetic Sweeteners

Sweetness is a characteristic of a great number of chemical substances of which some have no link with sugar. For example, lead acetate $Pb(CH_3COO)_2$ is not only very sweet but poisonous as well. Amazingly, the main artificial sweeteners were the results of *accidental* findings. They include: saccharin, cyclamates, aspartame, acesulfame, and sucralose. They have substituted to sugar for dietary purpose such diabetics. Their sweetness-related discoveries had been tied with tasting. Saccharin was *accidentally* came across in 1879 by Ira Remsen[13)] (1846-1927) and Constantin Fahlberg (a visiting research fellow in Remsen's Laboratory at John Hopkins University) while they were studying the effect of substituents on the oxidation of the alkyl groups of alkylated aromatics. The oxidation of the toluene substituted as shown in Eq. (4) led to the unexpected substance, the saccharin. Up until now, the industrial process of saccharin manufacture has been resting on the steps traced in this scheme. Not only was its synthesis accidental but also its sweet taste. On the one hand, Remsen tasted the piece of bread contaminated with the product and found it very tasty. It is good, at this point, to ponder on *the serendipity* of having a piece of bread nearby. Fortunately, the saccharin is devoid of high toxicity.[14)] The Remsen's excitement was immeasurable when he found out that its sweetening power overweighed that of ordinary sugar (see Table 2); an aqueous solution of saccharin retains its sweetness at a dilution as low as 10^{-5}. On the other hand, Fahlberg noticed this sweetness when he was eating his dinner. Amazed by this taste, he went back to the laboratory and remade the synthesis following the steps of the previous one, and, indeed, found the final product very sweet.

Four years later, Fahlberg patented this finding without mentioning Remsen name and became a wealthy person afterwards.



(4)

saccharin

In 1937, at the University of Illinois, Michael Sveda, while working as a graduate student under Audrieth's supervision accidentally discovered calcium cyclamate. Initially, he intended to make some anti-fever drugs. This time, it was through a cigarette which was contaminated with the product that the sweetness of this substance was noticed.

Table 2: Artificial Sweeteners

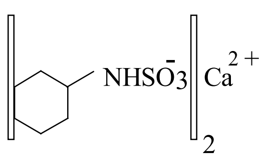
	Saccharin	Cyclamate	Aspartame	Acesulfame	Sucralose	Alitame
Sweetness potency Relative to sucrose	300	35-50	180	200	600	2,000
Year of discovery	1879	1937	1965	1967	1976	Developed by Pfizer in the 1980s

James M. Schlatter (S. D. Searle Company) fortuitously discovered aspartame in December 1965 while he was working on new treatments for gastric ulcers. The work was focused on making tetrapeptide compound which required a dipeptide intermediate from aspartic acid and phenylalanine (amino acids). Later, upon licking his finger, he remarked a sweet taste which he attributed to a doughnut he had eaten earlier; but, sooner, he realized that he had washed his hands afterwards. He then decided to taste the product and found it, in fact, sweet. Both his supervisor, Bob Mazur, and his colleague, Harman Lowrie confirmed the sweet taste of this substance. Here is a passage from the book *Aspartame: Physiology and Biochemistry* of James M. Schlatter, describing the fortuitous finding of the sweetness of aspartame:

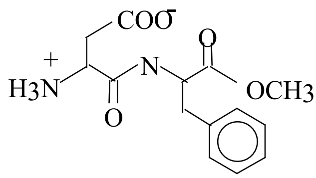
> *[I]n December 1965 I was working with Dr. Mazur on the synthesis of the C-terminal tetrapeptide of gastrin. We were making intermediate and trying to purify them. In particular, on an occasion in December 1965, I was recrystallizing aspartylphenylalanine methyl ester (aspartame) which had been prepared…and given to me by Dr. Mazur. I was heating the aspartame in a flask with methanol when the mixture bumped onto the outside of the flask. As a result, some of the powder got onto my fingers. At a slightly later stage, when licking my finger to pick up a piece of paper, I noticed a very strong, sweet taste. Initially, I thought that I must have still had some sugar on my hands from earlier in the day. However, I quickly realized this could not to be so, since I had washed my hands in the meantime. I, therefore, traced the powder on my hands back to the container into which I had placed the crystallized aspartylphenylalanine methyl ester. I felt that this dipeptide ester was not likely to be toxic and I therefore tasted a little of it and found that it was the substance which I had previously tasted on my finger.*

Acesulfame was accidentally discovered by Karl Clauss in 1967 (Hoechst AG Company). Clauss also noticed the sweet taste of this substance by licking his finger. Sucralose or Splenda was accidentally discovered in 1976, through a misunderstanding, by Shashikant Phadnis while he was working on halogenated sugar under the supervision of Leslie Hough at King's College in London who had a joint project with Tate & Lyle Ltd, a British sugar refiner.

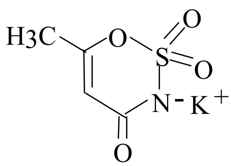
A matter of controversy is still going on as to whether the above artificial sweeteners are safe to consume. In awe with saccharin, Teddy Roosevelt claimed "*Anyone who thinks saccharin is dangerous is an idiot*". Although they have been widely used, aspartame, sucralose and acesulfame are claimed to be highly toxic.



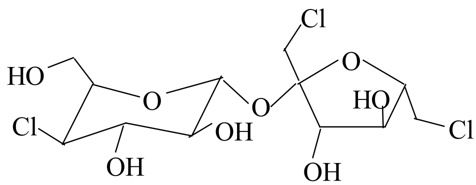
Cyclamate



Aspartame



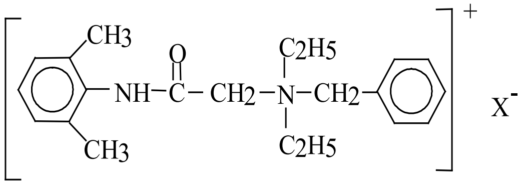
Acesulfame



Sucralose

Synthetic Bitter substance

If Alitame, an aspartame patent, is the sweetest molecule (cf. Table 2), the bitrex (denatonium benzoate, benzyl lignocaine benzoate) has been adversely the bitterest one until 1980.[15] The taste of bitrex was unexpectedly remarked according to Payne. In the 1950s, W. Barnes (T&H Smith Company, Edinburgh) conceived a chemical pathway for the synthesis of a new local anaesthetic using lignocaine as a starting material.



Lignocaine benzyl benzoate, X = benzoate
Lignocaine benzyl chloride, X = chloride

Bitrex

The quaternization of the latter followed by benzylation with benzyl chloride ended up with the product bitrex. While the expected anaesthetic property has been proven, the unexpected one, however, was its bitter taste. This bitterness was unpalatable and so poignant that it was detected only by smell; it can be even detected at concentrations as low as 10 ppb. It was fortunate with bitrex because it has substituted to the naturally bitter compounds, strychinine and brucine used in the homeopathic medicine. These substances are alkaloids extracted from *nux vomica* beans. Bitrex was found to be 50 times bitterer than brucine.

Bitrex displayed the following advantages over brucine: a) non-irritant and non-mutagenic, b) with a less interference with alcohol function, c) relatively less toxic, d) bitterness retention of aqueous and alcohol solutions over a long period of time (years), even after exposition to light.

To date, bitrex is widely used in: a) denaturing of alcohol, sugar, oil and tallow, b) aversive uses, to protect people from hazardous product, c) household products (detergents, aerosols, and shampoos), d) garden products (herbicides, insecticides).

Finally, it is quite interesting to know that these accidentally discovered substances, saccharin and bitrex with opposite taste-properties, are nowadays commercialized in one kit called "*Bitrex and saccharin fit test kits*".

Acknowledgements

I am grateful to Professor Hugo Kubinyi (BASF, Germany) for reading the "therapeutic molecules" part of this essay, and for his valuable comments and corrections. I also thank Philip Ball (a scientist writer and a consultant editor for the journal *Nature*) for sending me his documents and for his suggestions related to the "tinting molecules" part.

NOTES

* Prof. Dr. Saâd Moulay is a member of the Bulgarian Society for the Chemistry Education and History and Philosophy of Chemistry (CE&HPC), No. 119.

1. In 1910, Sharpey Shafer thought of a chemical missing from pancreas of diabetics. He even proposed the term "*insulin*" for this missing chemical, a term that was adopted by Banting.

2. Banting and his assistant Charles H. Best were the first to isolate insulin but the Nobel Prize went indeed to Banting and McLeod, the director of the institute who had just supported this research. In protest against the decision of the Nobel committee, they shared their Nobel Prizes with some colleagues, Banting with Best and McLeod with J. Bertram Collip, who had contributed to the purification of insulin.

3. In 1826, two Italians, Brugnatelli and Fontana, obtained *salicin* but in a highly impure form. In 1828, the German Johann Buchner was able to isolate a tiny amount of bitter yellow needle-like crystals, which he called *salicin*. In 1829, the French chemist Henri Leroux found a better extraction procedure and obtained about 30g from 1.5kg of bark. In 1838, the Italian chemist Raffaele Piria split

salicin into a sugar and an aromatic component (salicylaldehyde) and converted the latter, by hydrolysis and oxidation, to an acid of crystallized colorless needles, which he named *salicylic acid*.

4. It is claimed that Arthur Eichengrun, the Hoffmann's supervisor, had a part of credit in the aspirin discovery.

5. The name "*aspirin*" was suggested by Bayer Company; "*a*" from acetyl, "*spir*" from spiraea plant, and "*in*" the suffix given to a drug name.

6. A British surgeon Joseph Lister (1827-1912) conducted in 1870s almost the same experiment protocols. The importance of his work was not realized until 1928.

7. A valuable contribution of Robert B. Woodward in the penicillin issue was the elucidation of its real β-lactam-based structure (before the World War II), and this was strikingly achieved by means of only IR and UV spectroscopes.

8. Methylene blue is widely employed as an indicator in chemical titration work.

9. Unfortunately, Domagk missed the Nobel Prize in medicine in 1939 because the Nazi policy at the time did not permit him to travel to Sweden.

10. Earlier in 1933, *prontonsil* was also tested in a 10 month-old boy, as well as in a few other cases before Domagk rescued his own daughter.

11. This table is used from reference 3 with permission of its author, Professor Hugo Kubinyi.

12. Sulphamidochrysoidine is active only *in vivo* and not *in vitro* as corrected by Professor Kubinyi.

13. In 1879, Ira Remsen founded the "*American Chemical Journal*", which was later joined to *Journal of American Chemical Society*. He is well renowned for the nitric acid-copper story.

14. Had Remsen practiced the "taste test" with brevetoxin B (this molecule has been made in 1994 through 83 steps during 12 years, in 0.004% overall yield), he would have shortly passed away.

15. In 1980, *Atomergic chematals* firm patented the synthesis of denatonium saccharate (US Pat 4 652 577). This substance is five times bitterer than bitrex.

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