The role of serendipity in drug discovery

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Serendipity is one of the many factors that may contribute to drug discovery. It has played a role in the discovery of prototype psychotropic drugs that led to modern pharmacological treatment in psychiatry. It has also played a role in the discovery of several drugs that have had an impact on the development of psychiatry. "Serendipity" in drug discovery implies the finding of one thing while looking for something else. This was the case in six of the twelve serendipitous discoveries reviewed in this paper, ie, aniline purple, penicillin, lysergic acid diethylamide, meprobamate, chlorpromazine, and imipramine. In the case of three drugs, ie, potassium bromide, chloral hydrate, and lithium, the discovery was serendipitous because an utterly false rationale led to correct empirical results; and in case of two others, ie, iproniazid and sildenafil, because valuable indications were found for these drugs which were not initially those sought. The discovery of one of the twelve drugs, chlordiazepoxide, was sheer luck.

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Definition of serendipity

Serendip is the old Arabic name for Ceylon, now known as Sri Lanka. The origin of the word "serendipity" is in a Persian fairy tale, The Three Princes of Serendip, whose traveling heroes were "always making discoveries, by accidents and sagacity, of things they were not in quest of."[1] In the 16th century, the tale was translated from Persian to Italian, and from Italian to French. Horace Walpole (1717-1797), an English man of letters, encountered it in a collection of oriental tales in French, and coined the English term "serendipity" in a letter to his friend, Horace Mann, dated June 28, 1754.[2]

Today, the word "serendipity" is a word that is used in everyday language. The *Oxford English Dictionary* defines it as "the faculty of making happy and unexpected discoveries by accident," and *Webster's New Collegiate Dictionary* as "the faculty of finding valuable or agreeable things not sought for."[3] In *Stedman's Medical Dictionary* "serendipity" refers to "an accidental discovery;" ie, "finding one thing while looking for something else."[4]

According to the Doctor Out of Zebulon column in the *Archives of Internal Medicine*, "serendipity signifies a mental state in which serenity and stupidity are blended," as for example, "the serendipity of a cow chewing its cud under a shady tree," or "the sort of thing that happens to you when on a dull day collecting fossils you find instead a beautiful woman who proves to be neither geologist nor archeologist."[5,6] However, this definition is erroneous, at least insofar as scientific discoveries are concerned. No scientific discovery has ever been made by pure luck. All happy accidents in science have one point in common: "each was recognized, evaluated and acted upon in the

Selected abbreviations and acronyms

5-HT	*serotonin*
CPZ	*chlorpromazine*
LSD	*lysergic acid diethylamide*
MAO	*monoamine oxidase*
NO	*nitric oxide*

light of the discoverer's total intellectual experience."[7] "Chance favors the prepared mind," as Pasteur (1822-1896) said, or more precisely: "Dans les champs de l'observation, le hasard ne favorise que les esprits préparés."[8] Indeed, it is hard to think of a better expression of "serendipity" as one reviews the incredible concatenation of intentional and chance events in medicine's happy accidents.[2,9]

Development of the drug industry

The story begins in 1856 with an 18-year-old English chemist named William Henry Perkins (1838-1907) who was trying to synthesize quinine and ended up with a bluish substance, that he extracted from a "black mess" in his test tube, which had excellent dyeing properties.[10] Perkins' discovery of the first artificial dye in history, variably referred to as aniline purple, tyrian blue, or mauve, triggered a chain reaction by serendipity.[7] Modifications of his process led to the development of many dyes and the emergence of the dye industry, eg, Bayer (1862), Ciba (1859), Geigy (1859), and Sandoz (1862).[10,11] Recognition that a fuller exploitation of his findings would require a new breed of chemist[12] gave a strong impetus for the development of organic chemistry.[13,14] The synthesis of organic compounds led to the birth of the pharmaceutical industry.[15] By the end of the 19th century, many of the dye companies, eg, Bayer (1896) and Ciba (1889),[12] extended their activities to the development of drugs.

Perkins' discovery cannot be attributed to pure luck. He studied at the Royal College of Chemistry in London under August Wilhelm von Hofmann (1818-1892), one of the pioneers of aniline chemistry,[16] and was aware that crystalline (a substance obtained by O. Unverdorben in 1826 by distillation of indigo) and kyanol or cyanol (a substance isolated from coal tar by F. Runge in 1834, that produced a beautiful blue color on treatment with calcium chloride), were the same substance (phenylamine, with the composition of $C_5H_5NH_2$) that C. J. Fritzsche obtained by treating indigo with potassium chloride, and named aniline. (The word "aniline" comes from *Indigofera anil*, the indigo-yielding plant; anil is derived from the Sanskrit word "nile," ie, dark blue.[17]) His serendipitous discovery was built on his knowledge and past experience. He was also fully aware of the potential use of his discovery.

Early drugs in psychiatry

The introduction of the first effective drugs for the control of excitement, agitation, and insomnia paralleled the birth of the pharmaceutical industry. In the clinical development of at least two of these drugs, potassium bromide and chloral hydrate, serendipity played an important role.

Potassium bromide

Potassium bromide is the oldest widely used sedative in medicine. It is the potassium salt of bromine, a chemical element, first isolated in 1826 from the ashes of seaweed by A. J. Balard, an apothecary in Montpelier, France.[18] In its natural form bromine is too corrosive to be ingested. As a potassium salt it is well tolerated.[19]

French clinicians believed that bromine was a substitute for iodine, and began using potassium bromide in a variety of disorders without tangible therapeutic effect. In 1857, 31 years after bromine was isolated, Charles Lockock, a London internist, discovered the anticonvulsant and sedative action of the drug.[20] His discovery was one of the many quaint examples of serendipity in which an utterly false theory led to correct empirical results. Lockock, like most physicians of his time, believed that there was a cause-effect relationship between masturbation, convulsions, and epilepsy. Bromides were known to curb the sex drive. Lockock's rationale was to control epilepsy, ie, convulsions, by reducing the frequency of masturbation.[21] The treatment was a success insofar as control of convulsions was concerned. It also brought to attention the sedating properties of the drug.

During the second half of the 19th century, potassium bromide and other inorganic bromide salts were widely used as anxiolytic sedatives and anticonvulsants.[22] They were undoubtedly effective, although their relatively low therapeutic efficacy coupled with high toxicity have today all but eliminated them from clinical use.[23]

Chloral hydrate

Similar to potassium bromide, the discovery of the sedative and hypnotic properties of chloral hydrate was also

the result of an erroneous idea, but in this case of a chemical theory.
Chloral, or trichloroacetaldehyde, was first prepared in 1832 by Justus von Liebig, a professor of chemistry in Giessen (Germany).[24] It was about 37 years later, in 1869, that its hydrate, chloral hydrate, was introduced into clinical therapeutics by Otto Liebreich, a professor of pharmacology in Berlin.[25] Liebreich assumed that one of the components into which chloral hydrate splits in the body is chloroform, and since chloroform induces sleep, so would chloral hydrate. Although no chloroform resulted from the degradation of chloral hydrate, chloral hydrate became the first synthetically produced reliable hypnotic; today, after almost 140 years, it is still used in clinical practice.[17]

Lithium in mood disorders

This discovery and rediscovery of the therapeutic effects of lithium in psychiatry were the result of false theories about the etiology of mood disorders.

Discovery in the 1880s

Lithium is an alkali metal that was discovered by J. A. Arfvedson in 1817 while analyzing the mineral petalite. The name lithium comes from the Greek "lithos," stone; it was coined by Jons Jacob Berzelius (1779-1848), who was involved in classifying minerals.[26] The substance was first isolated in sufficient quantity for medical use by R. Bunssen and A. Mathiessen, in 1855. Four years later, after the demonstration that lithium carbonate could dissolve urate stones,[27] the substance was introduced into medicine for the treatment of gout by Alfred Barring Garrod.[28] Gout is a disease with urate deposits in the cartilage and increased uric acid, a breakdown product of urea, in the blood.
During the second part of the 19th century, many physicians believed in a uric acid "diathesis," a predisposition for the accumulation of urea in the body,[29] that could cause a variety of disorders from gout and rheumatism to cardiac disease and mental illness.[27] Since acute symptoms of gout develop suddenly and persist untreated for days or weeks before they remit, William Hammond, at the Bellevue Hospital in New York, had assumed that mood disorders might be a form of cerebral gout and employed lithium successfully in their treatment.[30,31] On the basis of the same assumption, Carl Lange, a Danish neurologist, treated hundreds of patients with lithium and reported on its prophylactic effect in periodic mood disorders in 1896.[32] Yet, without the availability of the necessary technology for monitoring blood levels, lithium was too toxic a substance to be clinically employed.

Rediscovery in the 1940s

In the late 1940s the therapeutic effect of lithium in mania was rediscovered by John Cade, an Australian psychiatrist.[33] Operating on the assumption that manic-depressive illness is analogous to thyrotoxicosis and myxedema, he hypothesized that mania is a state of intoxication by a normal product of the body in excess, and melancholia is a state of deficiency of the same substance. To test this hypothesis he compared the effects of intraperitoneally injected concentrated urine from manic subjects with urine from normal subjects in guinea pigs, and found the former far more toxic in killing the animals than the latter. Cade identified urea as the culprit that killed the animals, and established that creatinine decreased ("protected") whereas uric acid increased ("enhanced") the toxicity of urine. Since the urine of manic patients was more toxic than could be neutralized by the protective action of creatinine, he decided to determine the toxicity-enhancing effect of uric acid. Because uric acid was virtually insoluble in water, he used the most soluble of the urates, lithium urate, in his experiments. To his surprise, instead of enhancing toxicity, lithium urate protected the animals from urea's toxic effects. He attributed the protective effect to lithium, and demonstrated that injection of an 8% urea solution killed five of 10 guinea pigs, whereas a similar solution with lithium added killed none.[34]
To determine whether lithium salts alone have any discernable effects, Cade injected large doses of 0.5% aqueous solution of lithium carbonate into guinea pigs, and found that after a latent period the animals became extremely lethargic and unresponsive to stimuli for about 2 hours. It may seem a long way from the lethargy of guinea pigs to the control of manic excitement, but since Cade's investigations had commenced in an attempt to demonstrate the presence of a toxic substance excreted in the urine of manic patients, he decided to compare the effect of lithium in ten manic, six schizophrenic, and five depressed patients. The substance was effective in controlling psychotic excitement, especially in manic patients.[33]

Cade's rediscovery of the therapeutic effect of lithium in mania led to systematic clinical investigations with the substance in the 1950s by Mogens Schou and his associates in Denmark, verifying the therapeutic effect of lithium in mania,[35] and rediscovering in the 1960s its prophylactic effect in manic-depressive psychosis and recurrent depression.[36] Since by the 1960s the substance could be safely administered, with the employment of the flame spectrophotometer for monitoring blood levels, lithium has remained the primary form of treatment in manic-depressive illness, referred to as bipolar disorder in current consensus-based classifications.[37]

The story of LSD-25

Cade's notion that mania is the manifestation of a toxic agent was in keeping with contemporary thinking about the biology of psychoses. One of the strong influences on the Zeitgeist was Rolv Gjessing's discovery in the mid-1930s of nitrogen retention in certain phases of periodic catatonia,[38] and his postulation that altered metabolism with the production of a mescaline-like substance was responsible for catatonia.[39] Another influence on the Zeitgeist was Swiss chemist Albert Hofmann's discovery of the psychotomimetic effect of lysergic acid diethylamide (LSD-25), a synthetic amide of the ergot alkaloid, lysergic acid,[40] in the early 1940s.

Ergot is a biological product of a growing fungus, *Claviceps purpura*, which had been used by women for inducing contractions of the uterus since the Middle Ages. It was introduced into medicine as a uterotonic by an American physician John Stearns in 1808.[41] Lysergic acid was first isolated from ergot by alkaline hydrolysis in 1933 by Jacobs and Craig.[42] In the late 1930s a new procedure was developed that allowed combining lysergic acid with amides in peptide linkage. It led to the first partial synthesis of a natural ergot alkaloid, ergometrine, a uterotonic, and, by modifying the alkanolamine side chain of ergometrine, to a synthetic ergot derivative, methergine, a hemostatic. In 1938, Hofmann, working in the laboratories of Sandoz, prepared lysergic acid diethylamide, a substance structurally related to the circulatory stimulant nikethamide, with the objective of developing an analeptic. Since the substance was the 25th compound of the lysergic acid amide series, it was given the code name LSD-25.[43] In pharmacological testing LSD-25 produced uterine contraction, similar to that of ergometrine. Excitation was observed in some animals after LSD-25 administration. The findings did not warrant immediate further exploration.

On April 16, 1943, while preparing a new supply of LSD-25, Hofmann was struck by a strange feeling that made him stop work in the mid-afternoon. He reported the following to his superior:

> …I was seized by a peculiar restlessness associated with a sensation of mild dizziness. On arriving home I lay down and sunk into a kind of drunkenness which was not unpleasant and which was characterized by extreme activity and imagination. As I lay in a dazed condition with my eyes closed (I experienced daylight as disagreeably bright) there surged upon me an uninterrupted stream of fantastic images of extraordinary plasticity and vividness and accompanied by the intense, kaleidoscopic play of colors. The condition gradually passed off after about two hours.[43]

Hofmann suspected that LSD-25 was the culprit, but could not figure how the substance "found its way into his body in sufficient quantity to produce such extraordinary phenomena." Moreover, the nature of his symptoms did not correspond with those previously reported with ergot poisoning. To get to the "root of the matter" he decided to conduct experiments with LSD-25 on himself. Since he took relatively high doses of the substance, the psychotomimetic effects were even more pronounced than on the first occasion.[43]

Although the discovery of the psychotomimetic effect of LSD-25 is usually attributed to serendipity, Hofmann maintains that "LSD was not the fruit of a chance discovery, but the outcome of a more complex process that had its beginnings in a definite concept, and was followed up by appropriate experiments, during the course of which a chance observation served to trigger a planned investigation, which then led to the actual discovery."[43] He was also aware that the discovery of the psychotomimetic effect of LSD "lent support to the hypothesis that certain mental illnesses that were supposed until then to be purely psychic in nature had a biochemical cause because it now seemed feasible that undetectable traces of a psychoactive substance produced by the body itself might produce psychic symptoms."[43]

In the mid-1940s, demonstration of the therapeutic effect of penicillin in primary syphilis and neurosyphilis with its implications for psychiatry distracted attention from Hofmann's discovery. It was more than 10 years later in the early 1950s that interest in LSD was revived after Woolley and Shaw's demonstration that it inhibited the neurotransmitter serotonin.[43] LSD became instrumental

also to the revival of experimental psychiatry in the mid-1950s because it is reasonable to assume, as Mayer-Gross pointed out, that psychological symptoms that can be provoked by a drug, can also be abolished by drug action.[39]"

Discovery of penicillin

The serendipitous discovery of penicillin in 1928 by Alexander Fleming led to major changes in the diagnostic distribution of psychiatric patients in the late 1940s.
Fleming was engaged in research on influenza when one of his staphylococcus culture plates had become contaminated and developed a mold that created a bacteria-free circle.[44] Since he was working in an old building with considerable dust, where contamination was likely to occur, many bacteriologists would not have thought it particularly remarkable that one particular colony of staphylococci was undergoing dissolution, for it has long been known that some bacteria interfere with the growth of others. However, Fleming recognized the possible significance of the bacteria-free circle,[45] and by isolating the mold in pure culture he found that it produced a substance that has a powerful destructive effect on many of the common bacteria that infect man. He named the antibacterial substance liberated into the fluid in which the mold was grown "penicillin," after *Penicillium notatum*, the contaminant of the staphylococcus colony that led to the dicovery.[46]
Although Fleming published his results in the *Journal of Experimental Pathology* in 1929,[44] it was only 10 years later that Howard Florey and his team embarked on the research that culminated in 1941 in the development of a methodology for the extraction and production of penicillin. To obtain sufficient quantity of the substance for clinical use, the original strain, *Penicillium notatum*, had to be replaced by *Penicillium chrysogenum*.[45] Two years later, John Mahoney and his associates in the US Public Health Service, demonstrated that penicillin was highly effective in the treatment of primary syphilis;[20] and in 1944, Stokes and his associates at Johns Hopkins Hospital in Baltimore, Maryland, reported on the therapeutic effect of penicillin in the treatment of "late syphilis including neurosyphilis."[47] Since neurosyphilis and infectious delirium represented a considerable proportion of psychiatric patients, by changing the diagnostic distribution of patients, the introduction of penicillin resulted in a shift in priorities in psychiatric research from the "organic" to the "functional" psychiatric disorders by the end of the 1940s.[17]

Anxiolytic drugs

The introduction of penicillin stimulated the industry to develop other antibiotics. The development of meprobamate, the first anxiolytic drug introduced into clinical practice, was the result of a serendipitous observation in the course of this research.

Meprobamate

Research that led to the development of meprobamate began in 1945 in the laboratories of the British Drug Houses Ltd (BDH) in London. Chemists were to develop nontoxic antibacterial agents that would inhibit the growth of Gram-negative micro-organisms that cause enzymatic destruction of penicillin. Since the only compound known at the time that had properties of this type was phenoxetol, the phenyl ethyl ether of phenol, Frank Berger examined several structurally related α-substituted ethers of glycerol—synthesized by William Bradley, the chief chemist of BDH—for their antibacterial and pharmacological action.[48] It was in the course of this research that Berger noted that "administration of small quantities of α-substituted ethers to mice, rats, or guinea pigs caused *tranquilization*, muscular relaxation, and a sleep-like condition from which the animal could be roused."[49] Impressed with the tranquilization and muscle relaxation produced by these drugs, Berger pursued his further research with mephenesin, or 3-(2-methoxyphenyl)-1,2-propanediol, the substance from the series that possessed the most intense muscle relaxant action and widest margin of safety.[50] Mephenesin was an old drug; it was first produced by the condensation of o-cresol with glycerine by Zivkovic in 1908.
Berger moved to the United States in 1948, and in the same year mephenesin was released for clinical use for muscular relaxation during light anesthesia, under the trade name Tolserol by E. R. Squibb. The drug was already in clinical use when it was recognized that it could relieve anxiety and tension. However, mephenesin had serious drawbacks, eg, short duration of action and greater effect on the spinal cord than on supraspinal structures. To overcome these disadvantages, Berger succeeded in initiating a program that yielded the synthesis of meprobamate, or 2-methyl-2-n-propyl-1,3-propanediol dicarbamate, by B. J. Ludwig, at the Wallace Laboratories of Carter Products, in May 1950.[48,51] The duration of action of the new drug was about eight times

longer than that of the parent substance. Similar to mephenesin, pharmacologically meprobamate was a tranquilizer. It depressed multineuronal reflexes without significantly affecting monosynaptic reflexes; counteracted pentylenetetrazol–induced convulsions, and produced a loss of the righting reflex in mice without causing significant excitement prior to the onset of the paralysis. In the spring of 1955 Lowell Selling was first to report on the therapeutic effect of meprobamate in anxiety and tension states. A few months later, in the summer of 1955, meprobamate was introduced into clinical use by Wallace Laboratories with the brand name of Miltown, the name of the small community in New Jersey where Berger lived at the time,[52] and by Wyeth Laboratories with the brand name of Equanil.[51]
By the late 1950s meprobamate was the most widely used prescription drug in the United States and in many other countries. It retained its lead until the late 1960s when it succumbed to diazepam, the second drug from the benzodiazepine series introduced into clinical use.[48,53]

Chlordiazepoxide

The synthesis of benzodiazepines is linked to the name of Leo Sternbach, a pharmacist and chemist working at Hoffmann-La Roche's research facility at Nutley, New Jersey (USA).
In the early 1930s Sternbach was a postgraduate student at the Jagellonian University in Cracow, Poland, and synthesized several heptoxdiazine compounds in an effort to develop synthetic dyes. In 1954, inspired by the phenomenal success of chlorpromazine and early reports on meprobamate, he resumed his research with heptoxdiazines with the hope of finding compounds with psychopharmacological activity.[54] In the course of this research he recognized that the drugs he perceived in the 1930s as heptoxdiazines were benzoxadiazepines, and synthesized about 40 benzoxadiazepine compounds. Although all of the newly synthesized drugs that were tested were pharmacologically inert, Sternbach decided to stabilize one of the benzoxadiazepines with methylamine, a primary amine, instead of using secondary or tertiary amines as in the pharmacologically inert derivatives. He labeled the stabilized compound Ro 5-0690, and placed it on the shelf. In 1957, Ro 5- 0690 was found, literally during a laboratory cleanup, and submitted for pharmacological evaluation, which showed that it had similar activities to meprobamate. This was sheer luck! Prompted by these findings, the structure of Ro 5-0690 was correctly identified as 1,4-benzodiazepine.
Ro 5-0690, the first anxiolytic benzodiazepine, was introduced into clinical use in 1960 with the generic name of methaminodiazepoxide (chlordiazepoxide), and the brand name of Librium. It was followed by the introduction of diazepam (Valium), another anxiolytic benzodiazepine, in 1963. From the late 1960s through the 1970s, sales of diazepam topped those of all other drugs in the United States.
The introduction of benzodiazepines vastly extended the use of psychotropic drugs, ranging from the treatment of schizophrenia, depression, and bipolar disorder to the alleviation of anxiety and other neurotic conditions, making psychotropic drugs one of the most prosperous businesses of the pharmaceutical industry.

Psychotropic drugs

The term "psychotropic" was coined by Ralph Gerard, an American neurophysiologist, in the mid-1950s,[17] for drugs with an effect on mental activity and behavior. During the 1950s, a series of new psychotropic drugs, such as chlorpromazine, imipramine, and iproniazid, were introduced. Their effectiveness in the treatment of schizophrenia, depression, and bipolar disorder was instrumental in shifting the site of psychiatric practice from psychiatric hospitals to the community.

Chlorpromazine

Chlorpromazine (CPZ), has a phemothiazine nucleus with a dimethylaminopropyl side chain. Synthesized by Paul Charpentier on December 11, 1950, in the Laboratories of Rhône Poulenc, at the time a major French pharmaceutical company, CPZ was released in May 1951 for clinical investigation as a potentiator of general anesthesia.[55]
The basic phenothiazine nucleus was synthesized by Bernthsen in 1883, and later introduced as an anthelminthic agent for the treatment of enterobiasis. Expectations that it might be effective in the treatment of protozoal infections were not fulfilled. Instead, Henri Laborit, a surgeon in the French Navy, at the Bizerte Naval Hospital in Sidi-Abdallah, Tunisia, found promethazine, one of the antihistaminic phenothiazines synthesized in the early 1940s, to be eminently suited for the prevention of surgical shock.[56,57] It produced "euphoric

quietude" with a "state of indifference" and when given prior to surgery patients remained "calm, somewhat somnolent, and relaxed."[58]

In 1950 Laborit moved from Bizerte to Paris and asked Dr Beal from the administration of Rhône-Poulenc for a somewhat similar phenothiazine to promethazine that could hopefully attenuate patients' anxiety while potentiating anesthesia. In 1951 he received a supply of CPZ for his clinical investigations. In February 1952 Laborit, in collaboration with Huguenard and Alluaume, reported that in doses of 50 to 100 mg intravenously, CPZ does not cause loss of consciousness or any change in the patient's mentation, but produces a tendency to sleep and disinterest in the surroundings.[57] In the same report Laborit recognized the potential use of CPZ in psychiatry.[59]

The first use of CPZ in a psychiatric patient was reported by Hamon, Paraire, and Velluz, at Val de Grace, the military hospital in Paris, in March 1952, about a month after the report of Laborit.[60] Before the end of the year there were several other reports, including the six papers by Delay and Deniker from the Saint Anne Hospital in Paris that set the stage for CPZ's development in psychiatry; there followed a report on the successful treatment of an aggressive paranoid patient by Follin, at Montauban Mental Hospital, in France, and an article on 20 psychiatric patients treated with CPZ, by Rigotti, in Padua, Italy. CPZ became available on prescription in France in November 1952 under the trade name of Largactil. Subsequently, within a short period of 3 years, from 1953 to 1955, CPZ treatment in psychiatry spread around the world.[54,61]

The first international colloquium on the therapeutic uses of CPZ in psychiatry was held in Paris, in October, 1955, with 257 participants from 15 countries.[62] The importance of CPZ was recognized by the scientific community in 1957 with the presentation of the American Public Health Association's prestigious Albert Lasker Award to the three key players in the clinical development of the drug: Henri Laborit, for first using CPZ as a therapeutic agent and recognizing its potential for psychiatry; Pierre Deniker, for his leading role in introducing CPZ into psychiatry and demonstrating its influence on the clinical course of psychosis; and Heinz E. Lehmann, from Canada, for bringing the full practical significance of CPZ to the attention of the medical community. In the same year Daniel Bovet was awarded the Nobel Prize in Medicine for his major contributions to the synthesis of antihistamines which, through Laborit's serendipitious discovery that an antihistaminic phenothiazine, promethazine, produced a state of detachment and indifference, led to the development of CPZ.[63]

Imipramine

The serendipitous discovery of the therapeutic effect of imipramine in depression was the result of search for a CPZ-like substance for the treatment of schizophrenia by Geigy, at the time a major Swiss pharmaceutical company. The discovery is linked to the name of Roland Kuhn, a Swiss psychiatrist, working at the cantonal mental hospital of Münsterlingen.

In the mid-1950s Kuhn suggested (to Robert Domenjoz, Geigy's director of pharmacological research) the testing of G 22,355, the dibenzazepine of the company with the closest structural resemblance to CPZ, with the hope that it would have similar therapeutic effects. The basic constituent, G 22,355, is the iminodibenzyl nucleus, synthesized in 1899 by Thiele and Holzinger. Kuhn's expectations were not fulfilled. The substance was ineffective in schizophrenia. Nonetheless, before returning his drug supply, Kuhn decided to try the substance in one of his female patients with severe endogenous depression. This led to the recognition on January 18, 1956, that G 22,355 may have antidepressant effects. Encouraged by his findings, Kuhn administered G 22,355 to two more female patients with severe endogenous depression. In both patients the drug had favorable effects. Furthermore, in all three patients discontinuation of treatment resulted in relapse, which was reversed by resumption of the medication. This prompted Kuhn to treat 40 more depressed patients with G 22,355 at the clinic. It was on the basis of his observations of these patients that he concluded that the drug is effective in endogenous depression, in which vital disturbance is in the foreground.[64] Kuhn attributed his discovery to his ability to recognize the depressive population responsive to the drug. As far as he was concerned, "chance" and "good fortune" were only contributing factors.[65]

Kuhn's first paper on the treatment of depressive states with an iminobenzylderivative, G 22,355 was published in the August 31st issue of the *Swiss Medical Journal* in 1957.[66] On September 2nd, he also presented his findings at the 2nd World Congress of Psychiatry in Zurich. By the end of the year, G 22,355, the first tricyclic antidepressant, was released for clinical use in Switzerland with the generic name of imipramine, and the brand name of Tofranil.

There was strong opposition by academic psychiatry to the drug treatment of depression in the late 1950s, but Kuhn prevailed, and the introduction of imipramine opened up the path for the development of other antidepressants.

Iproniazid

In the same year that Kuhn presented and published his findings on the antidepressant effect of imipramine, two independent groups of investigators, Loomers, Saunders, and Kline, and Crane, presented their findings on the therapeutic effect of iproniazid, a monoamine oxidase inhibitor, in depression, at a regional meeting of the American Psychiatric Association in Syracuse, New York.[67,68] Iproniazid, an isonicotinic acid hydrazide, was synthesized in 1951 by Herbert Fox at Roche laboratories in Nutley, New Jersey (USA) for the chemotherapy of tuberculosis. In 1952, using iproniazid in tubercular patients, Selikoff, Robitzek, and Orenstein noted that the drug produced euphoria and overactive behavior in some patients.[69] In the same year, Zeller and his associates revealed the potent monoamine oxidase-inhibiting properties of the drug.[70]

Monoamine oxidase (MAO) is the enzyme responsible for the oxidative deamination of neurotransmitter monoamines, such as serotonin (5-HT) and norepinephrine (NE). The presence of these substances in the brain was first shown in 1953 and 1954 respectively; and the instrument (spectrophotofluorimeter),with a resolution power to measure the concentration of these monoamines and their metabolites in the brain, was introduced in 1955.[71] One year later, in 1956, Brodie, Pletscher, and Shore found an increase in brain monoamine, ie, 5-HT and NE levels, after the administration of iproniazid.[72] Nathan Kline was first to attribute the antidepressant effect of iproniazid to MAO inhibition, ie, to the rise of 5-HT and NE levels in the brain.[73]

The combination of serendipity and science that led to the development of MAO inhibitors for the treatment of depression triggered the development of neuropsychopharmacology, the scientific discipline dedicated to the study and treatment of the pathophysiology of mental syndromes with the employment of centrally acting drugs.

Sildenafil

In the current psychopharmacological era in psychiatry, the scope of psychiatry is extended to dimensional anomalies of abnormal psychology. Ever-newer drugs for multiplying indications are introduced, and in the development of at least one of these new drugs, sildenafil, serendipity has played a role.

Sildenafil is a selective 5-phosphodiesterase inhibitor that dilates cardiac vessels by acting on cyclic-GMP. However, expectations in clinical investigations with sildenafil in the treatment of angina pectoris conducted by Pfizer, one of the major American pharmacological companies, were not fulfilled. Instead of relieving anginal pain, the drug induced unwanted penile erections in some patients.

Independently of Pfizer, Solomon Snyder and his associates at Johns Hopkins University were working with nitric oxide (NO), a substance responsible for the physiological relaxation of blood vessels. Suspecting that NO might be a neurotransmitter, the Johns Hopkins group conducted immunochemical investigation with NO synthase (NOS), the enzyme responsible for the production of NO. In the course of this research they found that NOS is localized in the penis; demonstrated that erections are blocked by NOS inhibitors, and suggested that NO is the transmitter of penile erection.[74] Since the action of NO is mediated by cyclic GMP, similar to that of sildenafil, the side effect of penile erection, reported by cardiac patients in the Pfizer study, was explained[75] by the findings of the Hopkins group.

Shifting the direction of clinical investigations with sildenafil from angina pectoris to erectile dysfunction led to the demonstration of the effectiveness of the drug in the treatment of male erectile disorder (*Diagnostic and Statistical Manual of Mental Disorders*, 4th ed - *DSM-IV*[37]), and to the marketing of sildenafil with the brand name of Viagra.

Conclusions

Serendipity is one of the many contributing factors to drug discovery. It has certainly played a role in the discovery of most of the prototype psychotropic drugs.

The discovery process includes the recognition of the potential of the findings on the basis of one's knowledge and past experience. As Johann Wolfgang Goethe (1749-1832), a discoverer himself, wrote: "Discovery needs luck, invention, intellect—none can do without the other."[65] ❑

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El papel de la casualidad en el descubrimiento de fármacos

La casualidad es uno de los múltiples factores que pueden contribuir al descubrimiento de fármacos. Ella ha jugado un papel en el descubrimiento de fármacos psicotrópicos prototipo, los que han conducido al moderno tratamiento farmacológico en psiquiatría, y también ha jugado un papel en el descubrimiento de algunos fármacos que han tenido un impacto en el desarrollo de la psiquiatría. La "casualidad" en el descubrimiento de un fármaco implica que se encuentra algo mientras se está buscando otra cosa. Esta fue la situación en seis de los doce descubrimientos casuales revisados en este artículo: la anilina púrpura, la penicilina, la dietilamina del ácido lisérgico, el meprobamato, la clorpromazina y la imipramina. En el caso de tres fármacos como el bromuro de potasio, el hidrato de cloral y el litio, el descubrimiento fue casual debido a un razonamiento completamente falso que llevó a resultados empíricos correctos; y en el caso de otros dos fármacos como la iproniazida y el sildenafil se debió a que se encontraron valiosas indicaciones para ellos, las cuales no se habían buscado inicialmente. El descubrimiento de uno de los doce fármacos, el clordiazepóxido, fue pura suerte.

Rôle du hasard dans la découverte médicamenteuse

La "sérendipité" ou hasard est l'un des nombreux facteurs qui peuvent contribuer à la découverte médicamenteuse. Elle a joué un rôle dans la découverte de prototypes de médicaments psychotropes qui ont conduit aux traitements pharmacologiques modernes en psychiatrie. Elle a également participé à la découverte de plusieurs médicaments qui ont eu un impact sur le développement de la psychiatrie. La "sérendipité signifie d'avoir trouvé une chose alors que l'on en recherchait une autre. Cela peut s'appliquer à la découverte de médicaments. C'est ce qui s'est passé pour six des douze découvertes fortuites décrites dans cet article, comme le pourpre d'aniline, la pénicilline, le diéthylamide de l'acide lysergique (LSD), le méprobamate, la chlorpromazine et l'imipramine. Pour trois médicaments comme le bromure de potassium, l'hydrate de chloral et le lithium, la découverte fut fortuitement heureuse car un argumentaire totalement faux a abouti à des résultats empiriquement justes ; et pour deux autres, l'iproniazide et le sildénafil, les indications de ces médicaments ne sont pas celles auxquelles on avait pensé au départ. La découverte de l'un de ces douze médicaments, le chlordiazépoxide, relève du hasard pur.

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