MS 10013

Review Article

Journal of Pharmaceutical Research Vol. 9, No. 2, April 2010 : 49-55.

ROLE OF SERENDIPITY IN DRUG DISCOVERY

Siddiqui S[1], Sharma S[2], Sharma B[3], Siddiqui AA*[2]

[1]Subramanium College of Science and Technology, New Delhi–110082.

[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), Hamdard Nagar, New Delhi-110062.

[3]Department of Pharmacy, Bundelkhand University, Jhansi (UP), India.

Received on : 13.03.2010 Revised : 19.04.10 Accepted : 20.04.10

ABSTRACT

Serendipity, in various shades of semantic legitimacy, is abundantly evident in history of drug discovery. In the present era, although new concept of rational drug design has been introduced even then, lots of drugs have arisen, and continue to arise, from chance observation and correct scientific methods. Chance does not produce drugs; but where chances have played a pivotal role in drug discovery, the event may be considered as serendipitous.

Keywords: *discovery; serendipity; penicillin.*

INTRODUCTION

In 1848, Pasteur observed the existence of sodium ammonium tartarate crystals in two enantiomeric forms. The salt of tartaric acid formed in wine cask was optically active, whereas, salt of racemic acid found in another stage of fermentation and with same composition is optically inactive[1]. He reported racemic acid salt with two kinds of crystals with similar shapes but nonsuperimposable. He separated out two types of the crystals on the left and right with tweezers. The solution of each crystal rotated the light in opposite directions, dextrorotatory and laevorotatory.

Pasteur was successful in this discovery because fortunate circumstances worked together. First, he had selected sodium ammonium tartarate which is one of the few salts that formed crystals at temperature below 26æ%C, at higher temperature only racemate crystallizes[1] and the night before this observation he left the sample of racemic acid in an open window i.e. temperature below 26æ%C so both optically active forms crystallized. Thus, serendipity is understood mainly due to accidental circumstances that surround it.

Louis Pasteur made many discoveries just by careful observations. On the basis of observations, Pasteur postulated in 1854, "In the field of observations chances only favors the prepared mind". There is a great saying "Chance unlocks a door, Most people just walk pass. A few with prepared mind open door and look inside the room". So, without an open mind it is not possible to exploit new possibilities.

As is widely known, the word "serendipity" came from Sir Horace Walpole's letter written on 28 January, 1754 to one of his friend, Walpole wrote about a silly fairy tale called "the three princes of serendip": as their highness traveled they were always making discoveries through "accidents and sagacity, of things which they were not in quest of"[2]. Walpole called these kinds of discoveries "instances of accidental sagacity" highlighting the accidental findings.

SERENDIPITY IN DRUG RESEARCH

Accidental discoveries always played an important role in science. The majority of the most important and revolutionary discoveries in biology and medicines have serendipitous element in them[3] especially in the search of new drugs serendipity plays a crucial role. Serendipity in drug discovery implies the finding of one thing while looking for something else. A few examples are penicillin, heparin, chlordiazepoxide, cisplatin, LSD, etc. The number of serendipitous findings in drug history is large (Table 1).

Penicillin

Penicillin is possibly the best known example of ancient serendipitous drug discovery. The discovery was made by Scottish scientist and Nobel laureate Sir Alexander Fleming in 1928. By 1928, Fleming was investigating the properties of *Staphylococci* and was in the middle of research on influenza. Fleming was already well-known from his earlier work, and had developed a reputation as a brilliant researcher. On 28th September 1928, Fleming returned to his laboratory having spent August on vacation with his family. Before leaving he had stacked all his cultures of *Staphylococci* on a bench in a corner of his laboratory. On returning, Fleming noticed that one Petri dish containing *Staphylococcus* plate culture he had mistakenly left open was contaminated by blue-green mould, which had formed a visible growth and that the colonies that had immediately surrounded it had been destroyed, whereas other colonies further away were normal. Instead of throwing the sample he did some research on it and concluded that the mould was releasing a substance that was suppressing the growth of the bacteria. Fleming isolated an extract from the mold and named it penicillin as it was a *Penicillium* mould, now known to be *Penicillium notatum*[4]. Fleming's previous experience in 1921 when he serendipitously discovered

***Correspondence :** anees_56@yahoo.co.in

a material (latter named as lysozyme by Fleming) in his own nasal mucosa that dissolved certain bacteria especially one called as *Micrococcus lysodeikiticus* plays an important role in his decision to conduct research on that dish.

Table 1: *List of Serendipitous Discoveries in Drug History.*

COMPOUNDS	ACCIDENTAL DISCOVERY
Acetylsalicylic acid	Irreversible enzyme inhibitor (vs. salicylic acid prodrug).
Aminoglutethimide	Breast cancer treatment (instead of antiepileptic).
Amphetamine	Stimulant (instead of nasal decongestant).
Chloral hydrate	Prodrug of trichloroethanol (instead of chloroform).
Chlordiazepoxide	Tranquillizer (unexpected chemical rearrangement).
Chlorpromazine	Neuroleptic (tested to prevent surgical shock).
Cinnarizine	Cardiovascular activity (predominant to antihistaminic).
Cisplatin	Cytotoxic effect of electrolysis product.
Cromoglycate	Antiallergic activity (accidental formation of chromone dimer).
Cyclosporine	Immunosuppressant (instead of antifungal agent).
Dichloroisoprenaline	β-blockade (instead of bronchodilation).
Dicoumarol	Anticoagulant.
Diethylstilbestrol	Estrogenic impurity of anol (dimerization product).
Diphenhydramine	Allergy treatment caused prevention of travel sickness.
Diphenoxylate	Antidiarrhoic (instead of analgesic).
Disulfiram	Hypersensitivity to alcohol.
Ether	Anesthetic activity in inhalation party.
Etomidate	Anesthetic activity (instead of chemotherapeutic).
Griseofulvin	Growth inhibition of conifers on certain soils.
Guanethidine	Antihypertensive activity (instead of antihyperosmotal drug).
Haloperidol	Neuroleptic activity (instead of analgetic).
Heparin	Deterioration of lipid coagulant unmasked anticoagulant.
Imipramine	Antidepressant activity (instead of neuroleptic).
Iproniazid	Antidepressant activity (instead of tuberculostatic).
Isoniazid	Tuberculostatic activity of organic intermediate.
Levamisole	Immunomodulating (instead of antiparasitic agent).
Lithium carbonate	Antidepressant activity of lithium urate.
Lysergide (LSD)	Hallucinogenic activity (instead of cardiovascular).
Meprobamate	Tranquillizer (instead of muscle relaxant).
Merbaphen	Diuretic activity (of an anti syphilitic agent).
Methaqualone	Hypnotic activity (instead of anti malarial activity).
Mifepristone	Antiprogestone activity (instead of glucocorticoid).
Nafftine	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 spasmolytic).
Phenylbutazone	Anti-inflammatory 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	Antiarrhythmic (instead of β-blocker).
Sulphamidochrysoidine	Prodrug of sulfanilamide (active only in vivo).
Tamoxifen	Antiestrogenic activity of 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.

At least 28 scientists before Fleming believed that mold killing one or two bacteria colonies during an experiment is an unfortunate error rather than opportunity for discovery[5]. For example Scott noticed the inhibition of staphylococcal colony by a mold; he viewed it as a nuisance. He also later said that Fleming's discovery was mainly attributable to his ability in grasping the opportunity others had let pass rather than due to just pure chance[6].

Despite this success, Fleming could not produce a concentrated extract of penicillin and so unable to prove its therapeutic value. At the same time Fleming's colleagues didn't take much interest in Fleming's discovery so the development of penicillin was delayed for ten years[7].

In 1939, Ernst Chain, Howard Florey, and Edward Abraham of Oxford University were able to purify and stabilize different forms of penicillin that enabled demonstration of its therapeutic potential. They miraculously cured mice infected with deadly pneumonia[8]. Again chances favored their work and serendipity played yet another major role. The species of animal they chose for laboratory studies turned out to be one of few species that do not find penicillin toxic. They used mice rather than guinea pigs; as penicillin is quite toxic to guinea pigs[9]. Had they chosen to work on guinea pig they might have deemed penicillin too toxic for use and mankind would have been deprived of the phenomenal life saving ability of this drug. They also thought that their extract was pure penicillin, in actuality it was only 1% penicillin and 99% impurities. Had the impurities been toxic, penicillin would have appeared dangerous, delaying further developments[10].

PSYCHOTROPIC DRUGS

Chlordiazepoxide

Chlordiazepoxide[11,12] was synthesized by Sternbach and Reeder in 1954. Chlordiazepoxide and related agents were formed when 6-chloro-2-chloromethyl-4-phenylquinazoline-3-oxide reacted with series of primary amines. Such reactions were expected to give secondary amine derivative of quinazoline derivatives. Unexpectedly, a ring enlargement occurred, yielding 2-amino derivative of 7-chloro-5-phenyl-3*H*-1,4-benzodiazipine-4-oxide in addition to the expected products. So when methylamine was used as primary amine, this side reaction yielded chlordiazepoxide[13]. So its discovery was accidental due to unexpected chemical rearrangement while preparing entirely different series of compounds. Randall and his co workers found out that chlordiazepoxide have interesting psycho sedative properties[14]. Chlordiazepoxide has muscle relaxant properties and sedative properties with very weak hypnotic activity. It also exerts marked taming and calming effects so it acts as potent tranquillizer.

Lithium Salt as Antimanic Drug

The use of lithium salts to treat mania was discovered accidentally by the Australian psychiatrist John Cade in 1949. Cade in late 1940s commenced investigation to demonstrate whether some excreted toxin could be detected in urine of some manic patients to cause mental symptoms. So he attempted to determine whether uric acid would enhance the toxicity of urea in guinea pigs. Cade needed soluble urate for a control. He used lithium urate, already known to be the most soluble urate compound, and observed that this caused the guinea pigs to become extremely lethargic and they seemed to be tranquilized. Soon, Cade proposed lithium salts as tranquilizers[15], and succeeded in controlling mania in chronically hospitalized patients with them. The patients treated by lithium showed noticeable improvement. Noack and Trunter treated around 100 patients suffering from variety of mental disorders with lithium with no serious toxicity[16]. This clearly shows that discovery of lithium as antimanic drug is also accidental. This was one of the first successful application of a drug to treat mental illness, and it

opened the door for the development of medicines for other mental problems in the next decades.

Chlorpromazine

In 1933, the French pharmaceutical company Rhone-Poulenc began to search for new antihistamines. In 1947, this company synthesized promethazine, a phenothiazine derivative, which was found to have more pronounced sedative and antihistaminic effect than earlier drugs[17]. A year later, the French surgeon Pierre Huguenard used promethazine together with pethidine to prevent surgical shock. Another surgeon, Henri Laborit, believed that compound used along with pethidine stabilized the central nervous system by sedating it[17]. He suggested to the Rhone-Poulenc that they develop a compound with better stabilizing properties. The chemist Paul Charpentier produced a series of compounds and selected the one with the least peripheral activity, known as chlorpromazine, a potent neuroleptic[18] So chlorpromazine was developed by chance observation by Henri Laborit.

LSD (Lysergic Acid Diethylamide)

LSD was synthesized on November 16, 1938 by Swiss Chemist Dr. Albert Hofmann at the Sandoz Laboratories in Basel, Switzerland as part of a large research program for reporting medicinally useful ergot alkaloid derivatives[19]. Psychedelic properties of LSD were discovered on 16 April 1943 accidentally when Hofmann decided to reinvestigate the LSD molecule that he synthesized 5 years ago. Hallucinations effect of LSD was found out when Hofmann accidentally ingested an unknown quantity of the chemical & felt restless and dizziness and had a strong desire to laugh for continuous six hours. Hofmann ingested 250 µg of LSD, so he hypothesized that 250µg would be the threshold dose based on the dosages of other ergot alkaloids. Sandoz Laboratories introduced LSD as a psychiatric drug in 1947 four year after its discovery by Hofmann.

Iproniazid

The discovery of iproniazid (1-isonicotinyl-2-isopropyl hydrazine) is an example of serendipity of great importance in the chemotherapy of mental illness. It was originally intended for the treatment of tuberculosis[20] due to presence of hydrazide moiety in its structure. In 1952, its antidepressant properties were discovered when researchers noted that the patients given iproniazid became "inappropriately happy". It was subsequently developed as an antidepressant and was approved for use in 1958. It was later withdrawn from the market in 1961 due to the unacceptable incidence of hepatitis[20]

Valporic Acid

Valproic acid (2-propylvaleric acid) was first synthesized in 1882 by Burton as an analogue of valeric acid, found naturally in crude drug, valerian[21]. Valproic acid is clear liquid fatty acid at room temperature, for many years its only use was in laboratories as a "metabolically inert" solvent for organic compounds. In 1962, the French researcher Pierre Eymard research student at University of Lyons, synthesized a series of derivatives of khellin as a part of doctoral studies. But when he tried to prepare the solution of the compound to be tested he could not dissolve it. He then sought advice from Helene Meunier of the Labartoire Berthier in Grenoble. She suggested using valporic acid as a solvent. The valporic acid did dissolve compounds and subsequent tests showed khellin derivatives to have potent anticonvulsant activity. Shortly after this, Meunier used valporic acid to dissolve a coumarin compound; it also proved to have anticonvulsant activity. She immediately tested valporic acid and discovered that it was an anticonvulsant, responsible for anticonvulsant activity[22].

ANTINEOPLASTIC DRUGS

Nitrogen Mustard

Discovery of nitrogen mustard or mechlorethamine gave birth to the field of anticancer chemotherapy. The drug is an analogue of mustard gas and was derived from chemical warfare research. In 1943 accident in Bari, Italy occurred while transporting nitrogen mustard, which exposed civilians and soldiers to it, it was noted that white cell counts of exposed patient's decreased[23,24], suggesting a possible therapy for the cancer Hodgkin's lymphoma. So by accident nitrogen mustard was discovered with anticancer activity.

Cisplatin

Discovery of anticancer drug, cisplatin is also an important example of serendipity playing important role in drug discovery. Its origin had nothing to do with cancer or drug. Biophysicist Barnett Rosenberg conceived the idea that electric currents may affect cell growth. He designed an experiment that passed an electric current through a soup of chemical nutrients in which bacteria grew. For electrodes he decided to use platinum, thinking that the inert metal would minimize spurious chemical effects. After two hours of electric current, the bacteria in the soup stopped dividing, instead, some continued to grow to enormous sizes. To pinpoint the cause of this phenomenon, he did numerous experiments, going into blind alleys and new directions. It turned out that his original ideas about electric current and platinum were both wrong. The current had no effect on bacteria growth and division. The platinum electrodes, under the experimental conditions, produced a trace amount of a rare compound *cis*-diammonia platinum chloride. It was this compound that prevented the bacteria from dividing. In his paper on this result, Rosenberg suggested that similar metal ions might also inhibit division of other bacteria or cells. If so, they could be useful in cancer

therapy by stopping cancerous cell division. This time his conjecture turned out to be right. Research along this line led to cisplatin[25] (marketed as Neoplatin), a treatment for a certain type of testicular cancer in men and ovarian cancer in women.

ARTIFICIAL SWEETNERS

Saccharin

Saccharin was first produced by Constantin Fahlberg, a Chemist working on coal tar derivatives in Ira Remsen's laboratory at the Johns Hopkins University. It was Fahlberg who, accidentally, discovered its intensely sweet nature[26]. While working in the lab, he spilled chemical on his hand. Later while taking dinner, Fahlberg noticed more sweetness in the bread he was eating. He traced the sweetness back to the chemical, later named saccharin[27], by tasting various residues on his hands and clothes and finally chemicals in the lab. By 1907, Saccharin was used as a replacement for sugar in foods for diabetics. Saccharin now is the foundation for many low-calorie and sugar-free products around the world.

Cyclamate

Cyclamate discovered accidentally by Michael Sveda in 1937, a graduate student in University of Illinois. While studying anti-fever drugs in laboratory, he put his cigarette down on the laboratory bench where he was working and found that it tasted sweet when he put it back in his mouth. This observation led to the development of cyclamate[28]. But unfortunately in year 1970 cyclamate was banned in the United States from use in foods, beverages and drugs, and is still currently banned. Despite this, more than 55 countries have approved the use of cyclamate.

Aspartame

Aspartame was discovered in 1965, by Jim Schlatter, a Chemist at G.D. Searle was working on a project to discover new treatments for gastric ulcers. One of the steps in the research process was to make a dipeptide intermediate, aspartyl-phenylalanine methyl ester. He accidentally and unknowingly spilled some on his hand. Later on, he licked his finger while getting a piece of paper, and noticed the sweet taste[29]. He decided to test the compound in coffee and confirmed the identity of the chemical with the sweet taste. The result was the sweetener, aspartame. Aspartame has a sweet taste with minimal bitterness. Its onset of sweetness may be slightly slower than sucrose, but the sweetness may linger.

Sucralose

Sucralose was also discovered accidentally in 1976 by Scientists, Tate & Lyle, working with researchers Leslie Hough and Shashikant Phadnis. On a late-summer day, Phadnis was told to test the powder. Phadnis thought that Hough asked him to taste it, so he did it and found the compound to be exceptionally sweet, as sucralose is 600 times as sweet as sucrose. This is how sucralose was also discovered in most bizarre way[30].

All of the above discoveries have one thing in common, they were unplanned. In each case, the workers were involved in research completely unrelated to their big discovery.

ANTHELMINTHIC DRUGS

Piperazine Citrate

Sometimes discovery of valuable therapeutic agents occur as a result of testing a drug candidate for an expected pharmacological effect and finding a quite different effect serendipitously. One of the most famous examples is development of piperazine citrate as potent and widely used anthelminthics. At end of the 19th century, piperazine was introduced as a treatment for gout because it forms a very soluble salt with uric acid. In the early 20th century this treatment was abandoned; but a Pharmacist in France had noticed that although treated patients may not have lost their pain, they often had lost their intestinal worms. Prompted by this chance observation, the welcome organization in Britain developed piperazine citrate into one of most widely used antihelmenthic of 20th century[31].

Levamisole

Levamisole (potent anthelminthic drug) was discovered serendipitously from chicken feces when Scientists at the Janssen Company in Belgium, screened synthesized compounds for their potential anthelmintic activity against worms in chickens[32]. During screening chemical compound (thiazothienol) was found out to be active against the worms, but not active against worm-infected rats and mice. Further experiments on chickens showed that the feces of the treated chickens contained a substance that was active against worms in rats and mice. Interestingly, it was not the original substance but was instead its metabolic product. That excreted substance (thiazothielite) was chemically modified to improve its efficacy and was developed as the veterinary drug tetramisole. The levo-isomer of tetramisole, named levamisole, was later found to have an improved safety margin, and was developed into an enormously successful anthelmintic agent[33] for use in livestock and, to a lesser extent, in humans.

IMMUNOSUPPRESSANT DRUGS

Cyclosporine

Cyclosporine was developed by Jean-Francois Borel (microbiologist) of Sandoz Laboratory in 1969. Cyclosporin was produced by *Tolypocladium inflatum*, *Trichoderma polysporun*, and *Cylindrocarpon lucidum*. Cyclosporin was developed at Sandoz Laboratory under the program for development of antifungal drugs but when sample was tested for antifungal properties it didn't produce effective results but by chance when

Sandoz was about to shut down that development program one sample of cyclosporin showed impressive immunosuppressant activity during an assay for immunosuppressive activity[34]. Cyclosporine now has become successful and potent immunosuppressant in preventing organ transplantation rejection.

ANTICOAGULANTS

Dicoumarol

Dicoumarol was discovered serendipitously by Frank Schofield, a Canadian veterinary pathologist, in 1921. In the early 1920s, lots of cattle's were hemorrhaging and bleeding to death. Frank Schofield observed that the cattle's ingesting moldy silage made from sweet clover is less or prone to hemorrhage so he assumed that sweet clover functioned as a potent anticoagulant[35]. He separated good clover stalks and damaged clover stalks from the same hay mow, and fed each to a different rabbit. The rabbit that had ingested the good stalks remained well, but the rabbit that had ingested the damaged stalks died from a hemorrhagic illness. This report led to the subsequent research that led to dicoumarol discovery. Dicoumarol was isolated and introduced in human therapy. Because of its narrow therapeutic range and its frequent side effects it was abandoned after a short period.

Warfarin

Warfarin (coumarone-based anticoagulants) was synthesized initially as rodent poison by the Wisconsin Alumni Research Foundation Research Chemist Karl Paul Link in 1948. In 1951, A US Army cadet unsuccessfully attempted suicide with warfarin (rodent poison) and recovered fully, this incident started new clinical studies for the use of warfarin as a therapeutic anticoagulant. It was found to be generally superior to dicoumarol, now has become the drug of choice to protect against stroke and other thrombotic diseases[36]. Recently it was also recognized as a possible lead for development of HIV protease inhibitors.

HAIR RESTORING DRUG

Minoxidil

Minoxidil was accidently discovered for its hair restoration properties. It was developed first as an anti-hypertensive-a drug designed to lower blood pressure by vasodilatation. It was, however, discovered to have an interesting side-effect. Minoxidil has an unexpected effect on the structure and cellular activity of hair follicles, and it increases the growth rate of hair. The effect of minoxidil on hair follicles varies from person to person-no effect in some people, substantial effect in others. Upjohn Corporation produced a topical solution that contained 2% minoxidil to be used to treat baldness[37] and hair loss, under the brand name Rogaine in the United States and Canada, and Regaine in Europe and the Asia-Pacific.

ANESTHETIC AGENTS

Etomidate

Etomidate is potent short acting anasthetic discovered by serendipity. In 1970s Janssen researcher screening imidazoles analogues for their chemotherapeutic activity found that one of them induced a profound hypnotic state in rats, whether injected or administrated orally. Nearly 50 analogues were then synthesized and screened. All showed hypnotic activity but it was transpired that etomidate (ethyl ester analogue of prototype methyl ester) is best anesthetic if used intravenously[38].

Nitrous Oxide

The anesthetic nitrous oxide (laughing gas), Initially well known for inducing altered behavior (hilarity), its properties were discovered when British chemist Humphrey Davy tested the gas on himself and some of his friends, and soon realized that nitrous oxide considerably dulled the sensation of pain, even if the inhaler were still semi-conscious. So it is then used as an anesthetic agent.

DRUG USED IN ERECTILE DYSFUNCTION

Sildenafil

Sildenafil citrate provides a modern and more famous example of drug discovery arising from the accidental exploitation of side effect. Sildenafil was synthesized by a group of pharmaceutical chemists working at Pfizer's research facility in England. Sildenafil was initially studied for use in hypertension and angina pectoris. Phase I clinical trials under the direction of Ian Osterloh suggested that the drug had little effect on angina, but that the treated patient exhibited an unexpected elevation in erectile function[39,40]. Pfizer therefore decided to market it for erectile dysfunction, rather than for angina. The drug was approved for use in erectile dysfunction by the US Food and Drug Administration on March 27, 1998, becoming the first oral treatment approved to treat erectile dysfunction in the United States[41].

ORAL CONTRACEPTIVES

Mifepristone

Mifepristone was discovered by researchers in France in 1980 while they were studying drugs acting on glucocorticoid receptor. During their research on glucocorticoid receptor antagonists they recognized its anti-progesterone activities and saw its potential for the induction of a medical abortion.

Norethindrone

Norethindrone was first orally highly active progestin synthesized accidentally by Chemists Carl Djerassi, Luis Miramontes, and George Rosenkranz in 1951[42]. Later, its ability to powerfully disrupt ovulation was recognized, and more importantly, it was found to be effective when taken orally.

Combined Oral Contraceptives Pills:

The first oral contraceptive Norethynodrel contained a minor estrogenic impurity mestranol (an intermediate in their synthesis) when it is clinically tested. Mestranol was serendipitously turned out to be prodrug of ethinylestradiol[43]. Pure norethynodrel caused some undesired preganancies; only the fortuitous combination of norethynodrel and mestranol proved to be safe contraceptive. The norethynodrel and mestranol combination was given under the proprietary name *Enovid*[44,45].

NON STEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs)

Aspirin

Acetylsalicylic acid was originally designed as a prodrug of salicylic acid to treat headache, fever and rheumatic arthritis. Much later it turned out to be being an irreversible cyclooxygenase inhibitor, preventing blood coagulation by the inhibition of thrombocyte aggregation[46].

Phenylbutazone

Phenylbutazone was developed as an acidic solubilizing agent for poorly soluble aminopyrine as it was structurally related to aminopyrine. Later it was found to be having anti-inflammatory properties of its own[47].

LAXATIVES

Phenolphthalein

Phenolphthalein was discovered to be a potent laxative, when it was tested as a possible marker to label cheap Hungarian wines[48]. The workers labeling wine experience laxative action of phenolphthalein.

CONCLUSION

Serendipity always plays an important and crucial role in drug discovery process over so many years and it will continue to play important role in near future as well. The history of discovery is “full of arrivals at unexpected destinations and arrivals at the right destination using wrong boat”. Drug discovery involves a balance between scientific methods and chances in all of its forms, so by cultivating and adapting aptitude for serendipity, researchers can greatly enhanced their investigative powers.

REFERENCES

1. Kempe DS. In *Organic Chemistry.* eds. New York: Worth, 1980, p 172.
2. Remer TG. In *Serendipity and the three princes.* eds. Norman (Oklahoma): Oklahoma University Press, 1965, p 6.
3. Beveridge WIB. In *The Art of Scientific Investigation*. eds. New York: W. W. Norton 1957, p 31.
4. Fleming A, *et al*. Brit J Exp Path. 1929; 10: 226.
5. Macfarlane G. In *Alexander Fleming: The Man and the Myth*. Eds. Cambridge: Harvard University Press, 1984, chs. 12, 13.
6. Scott WM. In *Veterinary Record,* 1946; 59: 680.
7. E. Chain. *et al*. Proc R Soc Lond. 1971; B179: 291.
8. Chain E, *et al.* Lancet. 1940; 2: 226.
9. Comroe JH, *et al.* Am Rev Resp Dis. 1977; 115: 853.
10. Taton R. In *Reason and Chance in Scientific Discovery.* eds. London: Hutchinson Scientific and Technical, 1957, p 85.
11. De Stevens G, *et al.* Prog Drug Res. 1986; 30: 189.
12. Sternbach LH, *et al*. Prog Drug Res. 1978; 22: 229.
13. Sternbach LH, *et al.* J Org Chem. 1961a; 26: 1111.
14. Randall LO, *et al*. J Pharmacol Exp Ther. 1960; 129: 163.
15. Cade JFJ, *et al.* Med J Aust. 1949; 2: 349.
16. Noack CH, *et al* Med J Aust. 1952; 2: 219.
17. Laborit H, *et al.* Presse Med. 1952; 60: 206.
18. Charpentier P, *et al.* Comptes Rendus. 1952; 235: 60.
19. Dr. Albert Hofmann, *et al.* J Ott MAPS. 1969; 6: 69.
20. Maxwell RA, *et al*. In D*rug discovery.* eds. Clifton, New Jersey: Humana Press, 1990, p 455.
21. Burton BS, *et al*. Am Chem J. 1882; 3: 385.
22. Meunier H, *et al.* Therapie. 1963; 18: 435.
23. Krumbhaar EB, *et al.* J Am Med Ass. 1919b; 73: 715.
24. Krumbhaar EB, *et al*. J Med Res. 1919; 40: 497.
25. Rosenberg B, *et al.* Nature. 1965; 205 (4972): 698.
26. John H Wotiz, *et al. J Chem Educ.* 1978; *55* (3): 161.
27. Tarberll D, *et al.* J Chem Edu. 1978; 55(3): 162.
28. Jukes TH, *et al.* J Am Med Ass. 1976; 236(17): 1987.
29. Pavlova LA, *et al*. Russ Chem Rev. 1981; 50: 316.

30. Molinary SV, *et al*. Foods & Food Ingred J Jpn. 1999; 182: 6.

31. Goodwin LG, *et al.* Trans R Soc Trop Med Hyg. 1980; 74: 1.

32. Raeymaekers AHM, *et al.* J Med Chem. 1966; 9: 545.

33. Campbell WC, *et al.* ILAR J. 2005; 46: 352.

34. Henry T Tribe, *et al.* Mycologist. 1998; 12: 20.

35. Schofield FW, *et al.* J. Am Vet Med Ass. 1924; 64: 553.

36. Wolff ME. In *Burger's Medicinal Chemistry and Drug Discovery. Volume 1: Principles and Practice.* eds. New York: John Wiley and Sons, 1995.

37. Lucky AW, *et al.* J Am Acad Dermatol. 2004; 50: 541.

38. Godefroi EF, *et al.* J Med Chem. 1969; 12: 784.

39. Boolell M, *et al*. Int J Impot Res. 1996; 8(2): 47.

40. Terrett NK, *et al*. Bioorg Med Chem Lett. 1996; 6: 1819.

41. Kling, *et al*. J Mod Drug Discov. 1998; 1: 31.

42. Djerassi C, *et al*. J Am Chem Soc. 1954; 76 (16): 4089.

43. Sneader W, *et al*. Menopause Int. 2000; 6: 129.

44. Rock John Garcia, *et al.* In *Proceedings of a Symposium on 19-Nor Progestational Steroids*. eds. Chicago: Searle Research Laboratories, 1957, p 14.

45. Pincus G, *et al.* Am J Obstet Gynecol. 1958; 75(6): 1333.

46. Jeffreys D. In *Aspirin: the remarkable story of wonder drug.* eds. London: bloomsbury publishing, 2004, p 233.

47. Wilhelmi G, *et al.* Schweiz Med Wochenschr. 1950; 80: 936.

48. Meyers MA. In *Happy Accidents: Serendipity in Modern Medical Breakthroughs.* eds. New York: Arcade Publishing, 2007, p 48.