ESSENCE

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, MANGALAGIRI

PHARMACOLOGY BULLETIN

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FROM THE EDITORIAL DESK….

Welcome to the Third issue of 'ESSENCE' from AIIMS Mangalagiri...

Chance discovery or serendipity has been found to be responsible for the discovery of a significant number of all drugs in use today. The origin of the word "serendipity" is from a Persian fairy tale in which the three Princes' of Serendip, while travelling were "always making discoveries, by accidents, of things they were not in quest of." Today, "serendipity" is a word that is used in everyday language to mean "accidental discovery;" However, no scientific discovery has ever been made by pure luck. It requires both a chance event and the mental ability to understand the occurrence and realise its potential. Pasteur's comment on serendipity certainly holds true: *"Dans les champs de l'observation, le hasard ne favoriseque les esprits prepares."* ("In the field of observation, chance favours only the prepared mind."). We present a few examples of drugs which were discovered by serendipity.

The current issue also highlights the emerging field of Eco-Pharmacovigilance which deals with the hazardous effects of drugs on the Ecology and Environment. Drug use has become an inevitable part of our lives but it is imperative not to compromise with the balance of ecosystem on any grounds. Solutions need to be explored to save our planet from ill effects of these chemicals.

The current issue also discusses the recent drug approvals and also safety alerts of various drugs. Finally, the readers can test their pharmacology knowledge with the cross word puzzle on 'Drugs causing gynaecomastia'.

Happy Reading.

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SERENDIPITY IN DRUG DISCOVERY

PENICILLIN:

Penicillin is possibly the best known example of serendipitous/accidental/chance drug discovery. On 28th September 1928, Fleming returned from a vacation and noticed that one Petri dish containing Staphylococcus plate culture, he had mistakenly left open was contaminated by blue-green mould. The staphylococcal colonies that were immediately around the mold had been destroyed, whereas other colonies further away were normal. Instead of throwing the sample he tested it and concluded that the mould was releasing a substance or 'juice' 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.

Despite this success, Fleming could not produce a concentrated extract of penicillin and so was unable to prove its therapeutic value. At the same time Fleming's colleagues didn't take much interest in Fleming's discovery. Eventually after 10 yrs in 1939, Ernst Chain, Howard Florey, and Edward Abraham were able to purify and stabilize penicillin that enabled demonstration of its therapeutic potential. They miraculously cured mice infected with deadly pneumonia. 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. Had they chosen to work on guinea pigs they might have deemed penicillin too toxic for use and probably not proceeded any further. The discovery of Penicillin also underlines the importance of taking vacations, because if Alexander Fleming had not taken the vacation, the petri dish could not have got contaminated by mold and mankind would have been deprived of the phenomenal life saving ability of penicillin.

SILDENAFIL:

In the late 1980s, scientists at Pfizer sought to develop a drug that could treat angina, similar to nitrates, but lack any tolerance effects. They hypothesized that blocking the enzyme PDE5 (phosphodiesterase type 5) could lead to vasodilation and treat angina. By the early 1990s, Pfizer began experimenting with a compound known as UK-92480.During phase 1 trials, it was noted that while the drug had little effect on angina, men began reporting erections as an unintended side effect. Pfizer decided to perform further studies on men suffering from erectile dysfunction which showed benefit in this group. In 1998, Sildenafil (Viagra) became the first FDA approved oral medication for the treatment of erectile dysfunction.

CLOMIPHENE:

During the late 1950s researchers started investigating nonsteroidal anti-estrogens as antifertility agents to be used as a "morning after" pill. Initially, these drugs worked as exceptional anti-fertility agents in laboratory animals; however when investigated in humans, paradoxically they were found to actually induce ovulation in sub-fertile women. This baffled the researchers who investigated further and the feedback mechanism between estrogen and FSH/LH was unraveled. Clomiphene was the nonsteroidal anti-estrogen that later received FDA approval for inducing ovulation in infertility cases. So, clomiphene which was being tested as an anti-fertility agent paradoxically is now used to help women gain fertility. That's a real 180 degree turn.

WARFARIN:

Warfarin is a vitamin K antagonist used as an anticoagulant and prevents stroke in high risk individuals. The history of warfarin dates back to the early 1920s when cattle in the northern USA and Canada became afflicted by an outbreak of a previously unrecognized disease that resulted in fatal internal bleeding. It was soon discovered that the cattle were ingesting moldy silage made from sweet clover hay, which was shown to contain a hemorrhagic factor that reduced the activity of prothrombin. Ten years later, scientists in Wisconsin identified that the anticoagulant in the sweet clover was a derivative of coumarin.

Further research was conducted to synthesize various coumarin derivatives. In 1952, one was approved as rodent poison. Several years later, attention shifted to human use after scientists identified that warfarin had a number of favorable chemical properties. At the time, anticoagulants such as heparin had to be given intravenously while others had a long onset to action. Further clinical studies reaffirmed the clinical benefit of warfarin as an anti-coagulant in humans. Notably, the name warfarin is derived from *WARF* (Wisconsin Alumni Research Foundation) and *-arin* from coumarin.

MINOXIDIL:

Minoxidil's history dates back to the 1950s when it was initially studied to treat gastric ulcers. In preliminary animal studies, it failed to exert the properties researchers had hoped; however, they noted that the medication instead acted as a strong vasodilator, thereby reducing blood pressure. Scientists then produced different variations of the medication and began conducting clinical studies in hypertensive patients. In 1971, minoxidil was approved by the FDA for an emergency use protocol for severely ill patients, with a 2-week treatment duration. However, many clinicians exceeded the FDA's two-week recommendation. Soon after, cases of hypertrichosis (excessive hair growth) were reported in 60-80% of these patients. A topical formulation was soon developed and clinical trials for patients with alopecia began in 1978. Ten years later, the FDA approved minoxidil for treatment of alopecia.

IPRONIAZIDE & MAO INHIBITORS:

Iproniazide is one of the world's first anti-depressants synthesized in 1951, and used initially to treat tuberculosis. When clinicians found that some patients exhibited euphoria and hyperactive behaviour under the drug's influence, it was discovered that it is a "Monoamine Oxidase Inhibitor" – meaning it prevents the breakdown of monoamines, such as 5-HT (serotonin). This chance observation led the researchers to study MAO inhibitors in treatment of depression and led to the development of this important class of anti-depressant agents.

COMBINATION BIRTH CONTROL PILLS:

In the quest to produce a safe and reliable birth control pill, scientists in 1950s tested pills containing progesterone on women in Puerto Rico. The researchers saw that along with progesterone, the pills contained certain impurities and they worked to remove them. However, the removal of 'impurities' from the pills worsened (and not improved) study results, they realized that the impurity was actually oestrogen and that a pill combining the two hormones was the chemical key. Since then, combination of oestrogen and progesterone became widely used as oral contraceptive pills.

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2. Timothy O S. The unusual discovery of ten commonly prescribed medications. Available from http://Pharmacytimes.com/contributor/timothy-o-shea/2017/06. [Accessed on 04 Mar 2020]

Recent news/Updates from the world of medicines ……..

Lorcaserin removed from market due to safety concern

Lorcaserin, one of the most popular drugs for management of obesity was withdrawn by the United States - Food and Drug Administration (US-FDA). This was after a post- trial with more than 12,000 subjects which revealed that there was an increased occurrence of cancer with the use of Lorcaserin. In a Drug Safety Communication, the agency said "health care professionals should stop prescribing and dispensing Lorcaserin to patients and look for alternative weight-loss medicines or strategies for your patients."

All Medical devices to be treated as "drugs" from April 1, 2020

The central government (India) notified all medical devices as "drugs", effective from April 1, 2020 bringing a range of products from instruments (MRI equipment, defibrillators, dialysis machine, X ray machine)to implants, to even software intended for medical use in human beings or animals under the preview of the Drugs and Cosmetics Act, 1940. At present only 37 medical devices are notified as drugs.

This notification will require that companies to seek approval from the drug controller to manufacture, import and sell any medical device in the country. Besides they will have to follow other norms and regulations under the law. The move also paves way for regulation of prices of the medical devices under the Drugs Price Control Order (DPCO).

U.S. begins First Coronavirus Clinical Trial testing of 'REMDESIVIR'

The first clinical trial testing Gilead Sciences Inc's experimental antiviral drug, Remdesivir has started in hospitalized patients with coronavirus. The first trail participant is an American who was repatriated after being quarantined on the Diamond Princess cruise ship and the study is being conducted at the University of Nebraska Medical center in Omaha, according to the National Institutes of Health.

With the rapid surge in the development of pharmaceutical industry, there is a great focus on the environmental issues caused by the pollutants of pharmaceutical products. These environmental pharmaceutical pollutants include excretion of pharmaceuticals after human and veterinary therapeutic use. Many pharmaceutical chemicals are non-degradable, resist the acid environment in the stomach or long-lasting, and thus present a special risk where they enter, persist, and disseminate in the environment carrying the risk of entering the water supplies and the food chain which will ultimately make an unwitting re-entry into humans and animals.

"Ecopharmacovigilance" (EPV) is an emerging science concerning detection, assessment, understanding, and prevention of adverse effects related to the presence of pharmaceuticals in the habitat. EPV has been an area of novel interest with specific aim to identify and reduce environmental harm by pharmaceuticals in a coordinated and timely manner.

Exposure of humans and animals through environment can affect them in various ways. The foremost among them is microbial resistance as long term exposure to low dose antimicrobial agents through drinking water may herald resistance. The long-term exposure to these environmental pharmaceutical pollutants could be responsible for chronic toxic effects in animals and plants including, endocrine disruption, growth inhibition, disruption of ecosystems of microbes and other effect on the humans or animals, which may include cause cytotoxicity, mutagenicity, teratogenicity, and so on.

Till date, the potential effects of the pollutants of these pharmaceuticals products have been demonstrated on wildlife species. Vultures have been poisoned and even critically endangered because they ingested diclofenac when feeding on the carcasses of livestock. Similarly, male fish are becoming sterile due to contamination of water by ethinylestradiol. Even though there is no systematic study to show the definite toxicity from these environmental pharmaceuticals on humans; it is speculated that humans who are on the top of the food chain would be jeopardized through the environmental pharmaceutical pollutants. Already, studies have shown that the decreasing sperm count in men can be correlated with the increasing exposure to environmental drug pollution.

Further, monitoring of different species; the measurement, prediction, and identification of potential effects of pharmaceutical pollutants in the environment will help to improve scientific understanding of pharmaceuticals in the environment. This will help to formulate rules and regulation to curb the disposal of pharmaceutical pollutants and its effects on the environment.

The European Commission (EC) is currently reviewing data on pharmaceuticals in the environment and the potential impact on the environment and public health, including a review of the current legislation for human and veterinary drugs. It has been suggested that collaboration between industry, academia, and government for research will ensure that adequate levels of environmental protection were encouraged and will promote EPV in this scenario.

The perspective of EPV include environmental friendly design for green drug as well as green chemistry in the process development, promoting biodegradable products, reduction of emissions from manufacturing, imparting education on rational, the management of unused drugs, etc. These new EPV approaches have been introduced into the environment for monitoring drugs like antidepressants,antibacterials likeflouroquinolones, hormones, paracetamol, and diclofenac.

A mandatory provision needs to be made in the process of drug development to establish safety in the context of environment. Study of the impact of the pharmaceutical ingredient on environment should also form part of the drug approval process. It is already become mandatory to perform the Environmental Risk assessment (ERA) before seeking market authorization of drugs in the European Union.

Some other remedial measures proposed to reduce the amount of drugs entering the environment:

1. To reduce generation of pharmaceutical waste at the site of usage

2. To increase efficiency of sewage treatment plants

3. Use of Green pharmacy to combat environmental drug pollution

4. Developing better drug disposal programs to take care of expired/surplus drugs including Return to donor or manufacturer or proper disposal in Landfill or through Incineration.

5. Waste immobilization through Encapsulation and/or Inertization

It is imperative not to compromise with the balance of ecosystem even though drug use has become an inevitable part of our lives. In the modern world, though there is scientific advancement but still we lack the basic skill and technology to replace drugs with biopharmaceuticals in practice. The research community, EPA, FDA and pharmaceutical manufacturers should work together to design educational programs to better inform investigators, healthcare providers and patients about the potential environmental impacts of pharmaceutical use and appropriate disposal methods.

References:

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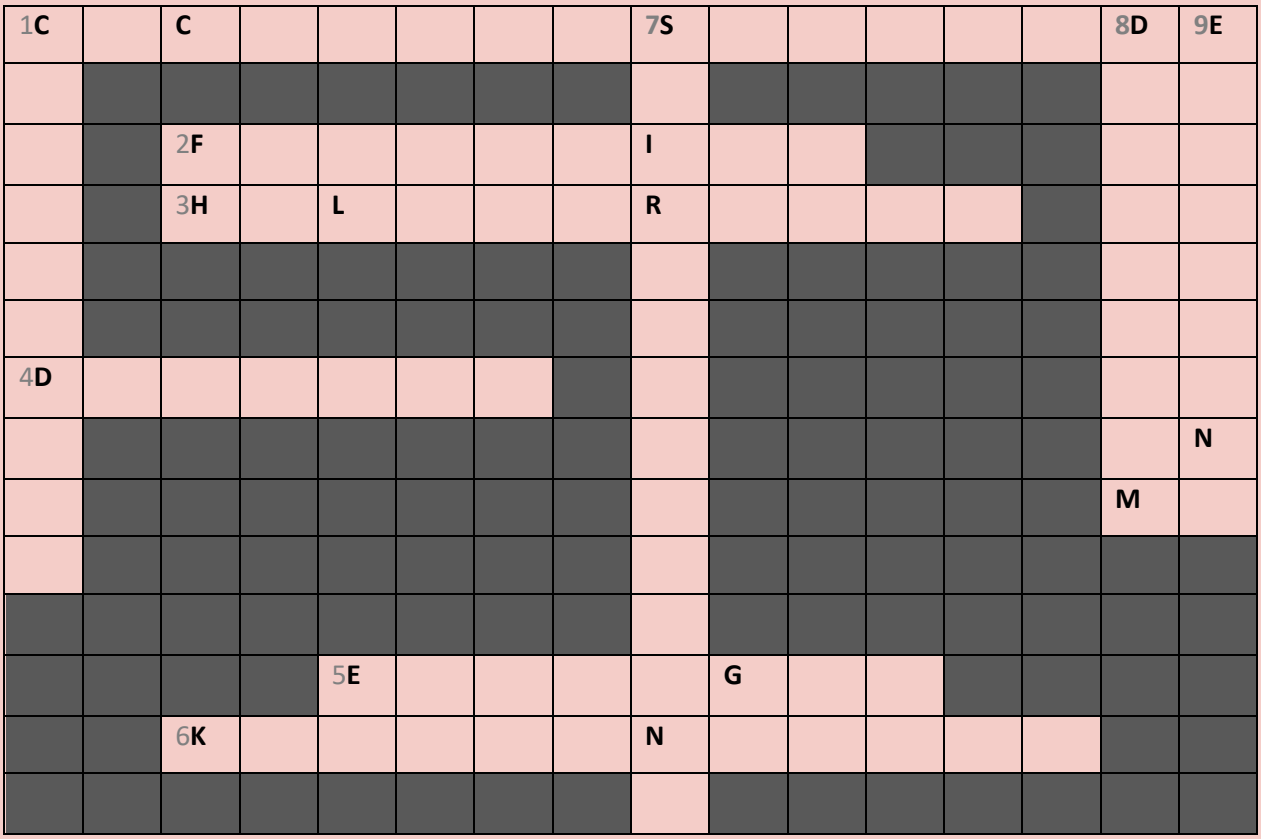
2. Gautam V, Sahni YP, Jain SK, Shrivastav A. Ecopharmacovigilance: An environment safety issue. The Pharma Innovation Journal 2018; 7(5): 234-9.

Be Cautious…..Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Chloroquine	Stevens-Johnson syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)
2.	Dabigatran	Vasculitis
3.	Cefotaxime	Eosinophilia and Systemic Symptoms (DRESS) syndrome
4.	Epirubicin	Pneumonia
5.	Moxifloxacin	Acute Generalized Exanthematous Pustulosis (AGEP)
6.	Montelukast	Neuropsychiatric Reactions

S. No.	Drug	Pharmacological Class	Indication	Dosage
1.	Pretomanid	Inhibition of mycolic acid biosynthesis	Multi-Drug Resistant (MDR) TB	200 mg/day
2.	Triclabendazole	Anthelmintic	Fascioliasis [Parasitic infestation due to Trematodes]	10 mg/kg [Total 2 doses at the gap of 12 hours]
3.	Istradefylline	Adenosine (A2A) receptor antagonist	Parkinson's disease (adjunctive therapy during OFF episodes.	20 -40 mg/day
4.	Solriamfetol	Dopamine & Norepinephrine Reuptake Inhibitor (DNRI)	Narcolepsy	75 mg/day
5.	Bremelanotide	Melanocortin receptor agonist	Premenopausal women with acquired, generalized Hypoactive Sexual Desire Disorder (HSDD)	1.75 mg/day; s.c
6.	Eptinezumab	Calcitonin Gene-Related Peptide (CGRP) antagonist	Migraine Prophylaxis	100 mg as an I.V infusion (In 100 ml normal saline) over approximately 30 minutes for every 3 months
7.	Ferric maltol	Iron replacement product	Iron deficiency anemia	30 mg Twice daily
8.	Romosozumab	Sclerostin inhibitor	Osteoporosis in postmenopausal women	210 mg s.c [Once every month for 12 doses]
9.	Siponimod	Selective sphingosine-1-phosphate receptor modulator	Multiple sclerosis	0.25 -2 mg/day
10.	Trifarotene	Retinoic Acid Receptors (RAR) agonist	Acne vulgaris	For Topical Use

Crossword Puzzle…
Hint: Drugs causing Gynaecomastia



Answers

Across

1. Anticancer drug having hemorrhagic cystitis is characteristic adverse effect (16)
2. Non- steroidal Anti-androgen drug used to treat prostate cancer (9)
3. Typical antipsychotic having extrapyramidal side effects(11)
4. Inotropic agent used for treatment of CHF(7)
5. Exogenous female hormone (8)
6. Broad spectrum antifungal agent (12)

Downward

1. H2 receptor antagonist used in peptic ulcer(10)
7. Potassium sparing diuretic acting on Distal convoluted tubule(14)
8. Calcium channel blocker belonging to Benzothiazepines group used in hypertension and arrhythmia (9)
9. Non nucleoside reverse transcriptase inhibitor for treatment of HIV(9)