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Serendipity in Paediatrics: a historical perspective of chance paediatric discoveries

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Abstract

Serendipity is the occurrence and development of events by chance in a beneficial way. Its role in medicine is frequently overlooked yet science and serendipity often go hand in hand. Many major breakthroughs were consequences of fortuitous chances and though often downplayed, failure to acknowledge its role in scientific advancement within clinical medicine is remiss. Far from simple happenstance, serendipity preferences the prepared and curious mind that knows to look to the spaces in between. This paper describes exemplars of serendipity in the development of modern paediatrics as we know it today; from developments in treatment such as the origins phototherapy for neonatal jaundice; to astute pattern recognition calling a halt to the use of thalidomide in pregnancy. The interplay of insight, observation and perpetual curiosity is paramount to progress, as these cases demonstrate.

Introduction

The word "serendipity" has its origins in a Persian fairy tale, The Travels and Adventures of the Three Princes of Serendip, in which the 3 heroic protagonists made discoveries by accidents or chance[1]. Horace Walpole, an English art historian came upon the fairy tale and coined the term "serendipity" in a letter written to a friend in 1754[2]. Today the word "serendipity" is a word that is used in everyday language and is defined as the occurrence and development of events by chance in a beneficial way[3].

The role serendipity plays in medicine is frequently overlooked yet science and serendipity often go hand in hand. Many major breakthroughs were consequences of fortuitous chances: penicillin[4], DNA[5], x-rays[6], anaesthesiology[7], earning three Noble prizes en route.

Like Newton being hit on the head with his proverbial apple—the steps leading to a new finding often tell a different story. Here we describe a few such exemplars which changed the face of paediatric medicine.

Phototherapy for Neonatal Jaundice

The story of how a little light came to be shed on jaundiced newborn infants is described by R.J. Cremer, who in 1956 was Registrar to R.H. Dobbs, Consultant Paediatrician at Rochford General Hospital, UK. The premature baby unit was disposed around a sunlit courtyard where on warm summer days, the sister in-charge would wheel the infants out as part of it's 'fresh air treatment' for premature babies[8].

On a particularly sunny day an infant was exposed for examination and noted to have a well demarcated triangle of jaundice on the abdomen. The rest of the skin was much less jaundiced. Dobbs thought it was iodine:

"I asked her, 'Sister, what did you paint it with - iodine or flavine, and why?' She replied that it must have been where the sun had faded the baby's skin, except where a corner of the sheet remained on the abdomen. We left it at that, and as the infant did well and went home, fresh air treatment of prematurity continued" [9].

A few weeks later and still during the warm summer, an extremely jaundiced infant had bloods taken and after a prolonged delay, the laboratory reported the serum bilirubin as 13-14mg/100ml. Convinced that this was wrong Dobbs sent another specimen and demanded an explanation for the delay in results. The biochemist found the tube lying on the windowsill after lunch. The new specimen level was 24mg/100ml however when he re-tested the old sample which was still lying on the windowsill in full sunlight, the level was even lower: 9mg/100ml. Dobbs describes how these two "happenings" prompted himself and Cremer to investigate the action of sunlight on bilirubin. Their findings were published in *The Lancet* in 1958 and are the lifeblood of medical therapy for jaundiced infants worldwide[10],[11].

Figure 1: Miss J Ward S.R.N in 1958, with one of the earliest of the infants given phototherapy at Rochford General Hospital, UK.[12]

Gluten Avoidance in Coeliac Disease

In the early 20th century it was generally agreed that the two main treatment principles in coeliac disease were rest and diet. Sidney Hass, in the most important study of this time (1936), reported ten patients, eight of whom treated by banana diet were cured, and the two untreated patients died[13]. Thus bananas were the staple diet of coeliac patients in this period.

Willem-Karel Dicke (1905-1962) was a Dutch paediatrician working in Juliana Children's Hospital in The Hague. He became convinced by the wheat free diet in 1936 after hearing a young mother's statement that her coeliac child's rash improved if she removed bread from the diet[14]. This was compounded during World War 2 when there was a shortage of bread. At this time Dicke ordered tulip bulbs to supplement the shortage of food in the hospital. Occasionally the children had rusks and the coeliac children became ill. His suspicions were reconfirmed when Allied aircraft dropped bread over occupied Holland and the coeliac children became ill again[15].

When Dicke moved to Wilhelmina Children's Hospital in Ultrecht he made a chance and fortunate friendship with JH van De Kamer, a biochemist who was the first to develop a method of measuring faecal fat content in wet faeces[16]. Together with HA Weyers, they developed a method that permitted the analysis of faecal fat excretion in children with coeliac disease by analysing the correct coefficient of fat absorption. Ensuing experiments led Dicke *et al* to conclude in 1950 that wheat flour was the cause of the anorexia, increased faecal output, and steatorrhoea seen in coeliac patients. They subsequently discovered that gliadin was responsible for the fat malabsorption in patients with coeliac disease. In the late 1950s Dicke went on to develop the gluten-free diet and in so doing, changed the treatment, prognosis and quality of life for children with coeliac disease worldwide.

Intravenous Potassium

In the early 20th century, physicians were not aware of the concept of extra-cellular fluid; what we now know as body fluid physiology[17]. The development of fluid therapy in paediatrics led the way in the introduction of body fluid physiology into broader clinical practice.

James Gamble and Daniel Darrow led this enterprise. Gamble initiated fluid therapy as effective treatment for diarrhoeal dehydration. Darrow extended the basic concepts of body fluid physiology by characterizing the osmotic control of water between extra and intra-cellular fluid[18].

Early paediatricians were stimulated by the extremely high infant mortality from diarrhoeal dehydration[19]. Between 1910-1940 various experiments were conducted by physicians including Hartmann, however a serendipitous encounter occurred in 1945 when Darrow and Gamble separately described two infants with metabolic alkalosis and diarrhoea from birth[20,21]. They demonstrated hypochloraemia, a high stool chloride concentration, and an absence of chloride in the urine. This remarkable simultaneous finding still bears the name Darrow-Gamble syndrome.

The two infants gave Darrow the idea that alkalosis was related to potassium deficiency. As a result, he reproduced potassium deficiency in rats in order to mimic the clinical state which he had observed. The results were published in the *Journal of Clinical Investigation* and the paper became a landmark article, drawing the attention of investigators to the role of potassium in the body economy[22]. Succeeding experiments conducted by Darrow have provided most of what we know about the role of potassium in the body, in part by taking infants out of orphanages in New Haven and bringing them into a clinical research unit where they were exposed to heat stress[23]. The results were remarkable. Darrow consequently was the first person to introduce intravenous potassium administration into clinical practice. The addition of potassium in parenteral fluid significantly improved survival rates in children with diarrhoeal dehydration[24] and the studies have resulted in what ultimately became the WHO oral rehydration therapy.

Congenital Prolonged QT Syndrome

A similar chance encounter provided an equally significant breakthrough in paediatric cardiology. Conor Ward, an Irish Paediatrician described the case of an 8-year-old girl referred to him in 1964 suffering from loss of consciousness of unexplained origin. In hospital she collapsed, pulseless, after running around the ward. Her brother was later affected. Their resting ECGs showed a prolonged QT interval; the episodes were caused by a serious form of ventricular arrhythmia.

"The textbooks proved of no help to me in trying to find an explanation for this and consultations with cardiologist colleagues worldwide initially proved fruitless until Anton Jervell told me about his finding deaf patients with the same condition in Norway" [25].

When Ward pursued the possibility of a genetic inheritance, they found a history of sudden cardiac death on the mother's side and her ECG showed QT prolongation. It was concluded that this cardiac syndrome had an autosomal dominant inheritance pattern[26]. Ward subsequently published this in the *Journal of the Irish Medical Association*[27].

Fortuitously, this article was picked up by *The Lancet* and published as an Annotation in 1964[28]. Perhaps even more fortuitously, the annotation was noticed by Caesarino Romano, an Italian cardiologist who had independently noted the same arrhythmia[29] and also recently published his findings in *The Lancet*. After publication of the eleventh case in 1970 the syndrome became associated with both their names and the eponym Romano-Ward adopted. Their serendipitous simultaneous publications inspired the experimental and clinical scientific acumen to detect the genetics, treatment and prevention of sudden death, one of the most significant causes of mortality today.

Propanolol for Capillary Haemangiomas

A chance discovery by a French paediatric dermatologist catapulted the use of propanolol to first line therapy for capillary haemangiomas. Christine Léauté-Labrèze was treating cardiomyopathy resulting from corticosteroid treatment for a haemangioma of the nasal pyramid in a 4-month-old patient. Soon after commencing propanolol she observed a change in the colour of the haemangioma and saw that it diminished in size. She first thought the improvement was a coincidence. However, three months later she noticed a similar effect after administering propranolol to a child who developed tachycardia after treatment with corticosteroids. The haemangioma softened and was greatly reduced in size[30,31]. This observation has resulted in the worldwide use of propanolol as first line treatment for capillary haemangiomas.[32]

Thalidomide

Even though events are unpredictable, types of events tend to occur regularly at particular times.[33] It is this patterned feature of events which enables us to make choices about what we observe and when we observe it. Such powers of observation may enable scientific breakthroughs to be made. What marks the insightful observer from the relaxed observer is the ability to recognise a pattern which has previously gone unnoticed and expose it.

This was such in the case of thalidomide, first created in 1953 for the treatment of morning sickness in pregnancy. By 1958, thalidomide was being heavily advertised and promoted around the world. However, in 1961, an Australian obstetrician began to notice cases of a congenital defect involving shortened or absent limbs in children at Crown Street Women's Hospital in Sydney. All of these mothers had used thalidomide in pregnancy[34]. Suspecting thalidomide to be the cause, McBride wrote a letter to the editor of *The Lancet* in the same year, detailing his concerns:

"Sir, congenital abnormalities are present in approximately 1.5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide during pregnancy…..to be almost 20%.

These abnormalities are present in structures developed from mesenchyme.... Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?"[35]

Around the same time, Widukind Lenz, a German paediatrician, had made similar observations and had already contacted the manufacturer of thalidomide about his concerns[36]. At this time there was generally accepted belief that the human placenta gave perfect protection to the foetus and was impervious to toxic substances except in such large doses that they killed the mother.[37] Thus thalidomide was considered safe. There were few experimental studies into the teratogenicity of drugs on animal models. Lenz and McBride's astute and powerful observation changed this. The drug was eventually withdrawn from the market, saving the lives of countless children worldwide. In 1964, three years after it was taken off the market, a novel test was discovered to identify teratogenic drugs in animal models. These are now a fixed component of the pre-clinical trials for every new drug produced worldwide.

Back to Sleep

Another insightful observation was made by David P Davies, a Welsh paediatrician who in 1985, was working in Hong Kong and noticed the low incidence of cot death there. He was surprised to discover how little awareness paediatricians in Hong Kong had about cot death. Noting the low incidence, he wrote a letter to the editor of *The Lancet* which was published in 1985[38]:

"Cot death is very rare in Hong Kong; this may be an important contributory factor to the low post neonatal mortality (3.1 per 1000). Over the 5 years 1980-84 only 15 cases of cot death were documented by forensic pathologists--an approximate incidence of 0.036 per 1000 live births. If the incidence was similar to that in western countries (2-3 per 1000), 800-1200 cot deaths might have been expected over this period. It is argued that this rare occurrence is real and not cot death masquerading as other causes of death. It is speculated that perhaps ….the practice of placing babies supine in their cots rather than prone……could contribute."

Davies postulated that supine sleeping was protective, as traditionally Chinese babies in Hong Kong were seldom put to lie in the prone position[39]. The front sleeping position had been recommended from 1943 and strikingly, no studies were published on the effect of sleeping position between 1970 and 1986. Davies' observations were confirmed in a prospective study published in 1989, of which he was an author[40]. Global interest was stimulated. In 1987 the Netherlands started a campaign advising parents to place their newborn infants to sleep in a supine position rather than prone[41]. International cohort and case-control studies in the early 1990s showed an increased risk of SIDS (three to nine times

higher) among babies who were sleeping prone[42],[43]. Worldwide campaigns to discourage prone sleeping were associated with a remarkable decrease in mortality due to SIDS of up to 70%[44],[45]. In 1992, the American Academy of Paediatrics (AAP) issued an official statement that healthy term infants should be placed to sleep on their back or side[46]. Since then, the "Back to Sleep" campaign has been adopted internationally and the powerful observation of Davies is now a firmly etched counsel for both parents and clinicians[47].

Haemorrhagic Disease of the Newborn

Vitamin K was first discovered by Danish biochemist Carl Peter Henrik Dam in the early 1930s[48]. Dam's initial interests lay not in coagulation but in cholesterol metabolism. In 1928 Dam began his study of the formation and metabolism of cholesterol. His key experiment involved feeding a cholesterol-free diet to chickens. He proved that, contrary to views at that time, chicks could synthesize cholesterol. During his studies, Dam incidentally noted that chickens that had been fed a certain fat-depleted diet showed signs of defective coagulation with spontaneous subcutaneous and intramuscular haemorrhages[48]. In 1932 scientists claimed that the disease he described was similar to scurvy and secondary to vitamin C deficiency. Dam however, attempted to reverse the bleeding through supplementation of feed with ascorbic acid and then with cholesterol, neither proving successful. In 1934 Dam announced that the bleeding was due to the absence in the diet of a hitherto unrecognised factor which he termed "the coagulation vitamin". This substance was later coined "Vitamin K" from the first letter of the Danish and German word for coagulation (*Koagulations-Vitamin*).

For his work, Dam was awarded the 1943 Nobel Prize in Medicine jointly with Edward Doisy for the discovery of Vitamin K[49]. Subsequently, the practical use of Vitamin K in medicine was studied. It is now almost 60 years since it was demonstrated in a series of 33,000 infants that vitamin K given to mothers antepartum could lessen the incidence of haemorrhagic disease in their newborn infants[50]. A single intramuscular dose at birth prevents almost all cases of haemorrhagic disease of the newborn, a life-threatening condition associated with high mortality and morbidity [51]. Now a standard of care in neonatology, a fortuitous incidental observation noted by a curious mind lies at the root of a preventative measure with significant improvement in clinical outcomes for our youngest patients.

Discussion

The history of medicine is replete with examples of serendipity and good fortune enabling scientific innovation. However, closer examination reveals that just like Newton being hit on the head with his proverbial apple, the steps leading to a new discovery often tell a

different story. It takes more than being in the right place at the right time to make a serendipitous discovery. Whilst the word itself is associated with such adjectives as “happenstance” “fate” and “chance”, psychologists have described a perceptual model of serendipity in which there are six essential components occurring in chronological order [53,54]: a well-prepared mind; an unplanned and unexpected event occurs; there is recognition of the potential for positive significance in the future; action is taken to increase the positive effect; over time the effects of the action become apparent; the value of the original unplanned event and the subsequent effects become apparent – at which time serendipity can be said to have taken place.

The examples given here though very different in their nature, all fit to this perpetual model. Many researchers may be reluctant to discuss their chance occurrences and findings, for fear of being perceived as a dilettante. The examples described here refute this and show the converse to be true: according to Pasteur "*in the observation field, chances will only favour well prepared minds*"[52]. Many perceived serendipitous discoveries take place only because the discoverer happened to have specialized background knowledge.

New innovations need creative thinking: often serendipity doesn't come from being the first to see something, but from being the first to see it in a new way. Such creative thinking can turn a routine observation into a scientific breakthrough. The right tools can also enable new findings: newer emerging technology allows us to study things in ways that weren't possible in the past.

Finally, the importance of good timing and a willingness for collaboration, or at the very least a shared acknowledgement, cannot be underestimated. Just like Gamble-Darrow and Romano-Ward, important discoveries are often made simultaneously by different people. They were certainly great thinkers of their own accord, but good timing contributed to their conceptual breakthrough.

And what about that famous apple? Contrary to popular belief, it didn't hit Isaac Newton, now famous for his theory of gravity, on the head. However, there is evidence that falling apples inspired him to think about the forces that attract objects towards Earth. Like Newton, the great discoveries in paediatric medicine provide examples of how planned insights coupled with unplanned events can potentially yield meaningful and interesting discovery in qualitative research.

Declarations of Conflicts of Interest:
None declared.

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References:

1. Remer T, Cristoforo Armeno. Serendipity and the three princes. Norman: University of Oklahoma Press; 1965.
2. Press.princeton.edu. 2021 [cited 4 November 2021]. Available from: http://press.princeton.edu/chapters/s7576.pdf
3. SERENDIPITY | Meaning & Definition for UK English | Lexico.com [Internet]. Lexico Dictionaries | English. 2021 [cited 4 November 2021]. Available from: https://www.lexico.com/definition/serendipity
4. Fleming A. On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to their Use in the Isolation of B. influenzæ. *Br J Exp Pathol*. 1929;10(3):226-236.
5. WATSON J, CRICK F. Genetical Implications of the Structure of Deoxyribonucleic Acid. Nature. 1953;171(4361):964-967.
6. The Nobel Prize in Physics 1901 [Internet]. NobelPrize.org. 2021 [cited 4 November 2021]. Available from: https://www.nobelprize.org/prizes/physics/1901/rontgen/biographical/
7. Insensibility during Surgical Operations Produced by Inhalation. The Boston Medical and Surgical Journal. 1846;35(19):379-382.
8. Watts G. Richard John Cremer. *The Lancet*. Volume 383, Issue 9931, Page 1800

9. Dobbs RH, Cremer RJ. Phototherapy. *Archives of Disease in Childhood*. 1975; 50:833-836
10. Cremer, RJ, Perryman, PW, Richards, DH. Influence of light on the hyperbilirubinaemia of infants. *Lancet*. 1958; 1, 1094.
11. Cremer, RJ, Perryman, PW, Richards, DH, Holbrook, B. Photosensitivity of serum bilirubin. *Biochemical Journal*. 1957; 66, 60P.
12. Dobbs RH and Cremer RJ. Phototherapy. *Archives of Disease in Childhood.* 1975, 50, 833.
13. Van Berge-Henegouwen GP, Mulder CJ. Pioneer in the gluten free diet: Willem-Karel Dicke 1905-1962, over 50 years of gluten free diet. *Gut*. Nov 1993; 34(11): 1473–1475.
14. Booth C. History of coeliac disease. *BMJ*. Feb 25, 1989; 298(6672): 527.
15. Pena AS. History of coeliac disease: Dicke and the origin of the gluten free diet. In: Mearin ML, Mulder CJJ (eds). Coeliac Disease, 40 years gluten free. Kluwer Academic Publishers; 1991. p1-9.
16. Van de Kamer JH, Huinink HTB, Weyers HA. Rapid method for the determination of fat in feces. *J Biol Chem* 1949;177:347–55.
17. Holliday M. Gamble and Darrow: pathfinders in body fluid physiology and fluid therapy for children, 1914–1964. *Pediatr Nephrol*. (2000) 15:317–324.
18. Chesney RW. Commentary on: The Maintenance Need for Water in Parenteral Fluid Therapy, by Malcolm A. Holliday, MD, and William E. Segar, MD, Pediatrics, 1957;19:823–832 *Pediatrics* Vol. 102 No. Supplement 1 July 1, 1998: 229 -230.
19. Darrow D. Grover Francis Powers and Pediatrics at Yale. *Yale Journal of Biology and Medicine.* 1952;24:242-251
20. Darrow, D. C. 1945. Congenital alkalosis with diarrhea. *J. Pediatr 1945;2*6:519.
21. Gamble SL, Fahey KR, Appleton J, Mac-Lachlan E. Congenital alkalosis with diarrhea. *J. Pediatr.* 1945;26:509.
22. Cooke R. Profile – Daniel C Darrow. *Journal of Pediatrics* 1966;69(3):490-495.
23. Cooke R, Pratt E, Darrow DC. The Metabolic Response of Infants to Heat Stress. *Yale J Biol Med.* Jan 1950; 22(3): 227–249.

24. Friedman A. Pediatric hydration therapy: Historical review and a new approach. *Kidney International* (2005) 67, 380–388.
25. Hunter N. A medical stalwart now in happy exile: Professor Conor Ward. *Irish Health*: 2021 [cited 4 November 2021]. Available from: http://www.irishhealth.com/article.html?id=18437
26. Ward OC. The electrocardiographic abnormality in familial cardiac arrhythmia. *Ir J Med Sci.* 1966;41:553–557
27. Ward OC. A new familial cardiac syndrome in children. *J. Ir. Med. Assoc*. 1964:54:103-6
28. Annotation. Congenital cardiac arrhythmia. *Lancet*. 1964;2:26-27?14
29. Luderitz B. Historical Perspectives of Cardiac Electrophysiology. *Hellenic J Cardiol*. 2009; 50: 3-16
30. Karmel M. Old Drug Offers New Approach to Infantile Hemangiomas. American Academy of Ophthalmology. *Clinical Updates in Pediatrics* 2010: 33-35.
31. Léauté-Labrèze, C. et al. *N Engl J Med.* 2008;358(24):2649–2651.2
32. Fette A. Propranolol in Use for Treatment of Complex Infant Hemangiomas: Literature Review Regarding Current Guidelines for Preassessment and Standards of Care before Initiation of Therapy. *Scientific World Journal*. 2013; 2013: 850193.
33. Phillips EB. Colonizing the World after Dark. *American Journal of Sociology. 1990; 95: 1089-1091*
34. Emanuel M, Rawlins M, Duff G, Breckenridge A. Thalidomide and its sequelae. *Lancet.* 2012; 380: 781-783
35. McBride WG. Thalidomide and congenital malformations. *Lancet*. 1961; 2: 1358
36. 'The History of Thalidomide' by Professor Dr. W. Lenz . Extract from a lecture given at the 1992 UNITH Congress. 2021 [cited 4 November 2021]. Available from: http://www.thalidomidesociety.co.uk/publications.htm
37. Dally A. Thalidomide: was the tragedy preventable?. *Lancet*. 1998; 351: 1197-1199
38. Davies DP. Cot death in Hong Kong: a rare problem? *Lancet.* 1985 Dec 14;2(8468):1346-9.

39. Lee N, Chan Y, Davies DP, Lau E, Yip DC. Sudden infant death syndrome in Hong Kong: confirmation of low incidence. *BMJ*. Mar 18, 1989; 298(6675): 721.
40. Engelberts AC, de Jonge GA, Kostense PJ. An analysis of trends in the incidence of sudden infant death in The Netherlands 1969-89. *J Paediatr Child Health.* 1991 Dec;27(6):329-33.
41. Fleming P, Guilbert R, Azaz Y, et al. Interaction between bedding and sleeping position in the sudden infant death syndrome: a population based case– control study. *Br Med J*. 1990;301:85–89
42. Dwyer T, Ponsonby A, Newman NM, Gibbons LE. Prospective cohort study of prone sleeping position and sudden infant death syndrome. *Lancet*. 1991;337:1244–1247
43. Dwyer T, Ponsonby A-L, Blizzard L, Newman NM, Cochrane JA. The contribution of changes in the prevalence of prone sleeping position to the decline in sudden infant death syndrome in Tasmania. *JAMA*. 1995;273:783–789
44. Court C. Cot Death in Britain: Incidence reduced by two thirds in five years. *BMJ.* 1995;310:7
45. American Academy of Pediatrics Task Force on Infant Positioning and SIDS. Positioning and SIDS. *Pediatrics*. 1992;89:1120–1126
46. Gelfer P, Cameron R, Masters K, Kennedy K. Integrating ''Back to Sleep'' Recommendations Into Neonatal ICU Practice. *Pediatrics.* 2013;131;e1264
47. Controversies Concerning Vitamin K and the Newborn Committee on Fetus and Newborn *Pediatrics.* Jul 2003, 112 (1) 191-192
48. DAM, H. The Antihemorrhagic Vitamin of the Chick.: Occurrence And Chemical Nature. *Nature.* 135, 652–653 (1935)
49. Dam, H., Dyggve, H., Larsen, H. & Plum, P. (1952) The relation of vitamin K deficiency to hemorrhagic disease of the newborn. *Advances in Pediatrics*. 5, 129–153.
50. Marc A. Shampo, Robert A. Kyle, Henrik Dam Discoverer of Vitamin K. *Mayo Clinic Proceedings.* Volume 73, Issue 1, 1998, Page 46.

51. Puckett RM, Offringa M. Prophylactic Vitamin K for Vitamin K deficiency bleeding in neonates. *Cochrane Database Syst Rev.* 2000;(4):CD002776.
52. The king of serendipity and the demise of phlogiston. The Story of Chemistry. NC Datta (ed) Universities Press.1st ed. 2005. p105.
53. Makri S, Blandford, A. Coming across information serendipitously: Part 1 – A process model. *Journal of Documentation*. 2012; 68 (5):684 - 705
54. Makri S, Blandford A. Coming across information serendipitously: Part 2 – A classification framework. *Journal of Documentation.* 2012; 68 (5):706 - 72