IJPT
1735-2657/11/102-92-96
IRANIAN JOURNAL OF PHARMACOLOGY & THERAPEUTICS

IJPT 10: 92-96, 2011

MINI REVIEW

Contribution of Women Scientists to Pharmacology: A Historical Perspective

NEETA DHAR GROVER

For author affiliations, see end of text.

Received March 27, 2011; Accepted June 12, 2011

This paper is available online at *http://ijpt.iums.ac.ir*

ABSTRACT

The article highlights the contributions of a few prominent women scientists to the science of pharmacology. These women,some of whom were from other scientific fields, contributed significantly to our understanding of pharmacology. This was achieved in an era in which pharmacology was a more or less male dominated field. Even though it is easier for women to enter scientific fields nowadays, the mid-career attrition rate seems to be high. There is still a lot of scope for improving the work environment and attitudes of the society in their favor.

Keywords: *Pharmacology, women, scientists, physiology*

"Many of these women faced enormous obstacles. They were confined to basement laboratories and attic offices. They crawled behind furniture to attend science lectures. They worked in universities for decades without pay as volunteers--in the United States as late as the 1950s"

-Sharon Bertsch McGrayne in Nobel Prize Women in Science

The above statement was made with respect to the women scientists who had to overcome many obstacles and had to repeatedly prove their worth in a male dominated field. Excellence in any field is a rare honour. If achieved by a woman in a hitherto male dominated field, it acquires even greater significance. The current article has been written with a view to highlighting the invaluable contribution of a few outstanding women to the field of pharmacology at a time when it was considered as a predominantly male domain.

Pharmacology in itself is a relatively new branch and was considered for quite some time as an offshoot of physiology and biochemistry. Many of the scientists mentioned in this article were not, strictly speaking, pharmacologists. Nevertheless, their work contributed immensely to the understanding of the subject and took it one more step towards making and shaping pharmacology into the science that it is today. Women in pharmacology, or any other science for that matter, were frowned upon and not taken seriously. In spite of this, in the very second meeting of the British Pharmacological Society, in 1932, held at University College London, a demonstration was given by Mary Pickford, the first woman to be elected as a member in 1935, and quickly followed by Edith Bulbring in 1936 and Marthe Vogt in 1937. Employment opportunities for women increased with the coming of the World War II, when men were needed on the front. But women still needed to give their first names in the abstracts whereas the male members only provided their initials. This bias was continued as long as 1975 [1].

Marthe Louise Vogt possessed a medical degree which she followed up with a doctorate in chemistry [2]. A formidable combination by all means. She migrated to Britain from Germany along with many scientists when the Nazis came to power. In 1935, she started work with Sir Henry Dale and another scientist, Feldberg (who had also migrated from Germany), in Dale's laboratory. Dale had already done extensive work on neurotransmission. Dale, Feldberg and Vogt demonstrated that acetylcholine is the substance released at motor nerve endings [3]. She published numerous papers on the role of adrenaline, dopamine and other neurotransmitters in the brain. After 1941, she concentrated her research on the adrenal gland and its relation to stress. At that time, the adrenal cortical hormones could only be estimated by indirect means like prolongation of survival time in adrenalectomized rats.Vogt determined the daily output of adrenal cortical hormones by collecting the venous effluent from the adrenal gland in five mammalian species [4]. The

effects of stress on the adrenal cortex were noted to be not completely abolished if the adrenal medulla had been removed first. This demonstrated that there was another factor, apart from adrenaline released from the adrenal medulla during stress that triggered the release of stress induced cortical hormones. Vogt by her experiments demonstrated the direct effect of adrenocorticotrophic hormone on the adrenal gland [5]. From the adrenals, she moved on to the central nervous system. This is believed to be a landmark publication describing the adrenaline and noradrenaline content of the various parts of the brain [6]. Later in life, she shifted focus to serotonergic transmission in the brain. She died in 2003 at the age of hundred.

Edith Bulbring was born in Bonn and she completed her medicine degree in Bonn University in 1928 [7]. She left Germany in 1933 and began working with J.H Burn at the Pharmaceutical Society in London and then in Oxford. She established herself as an accomplished physiologist. The techniques developed by her expanded on the, at that time, meagre knowledge of smooth muscle function. She demonstrated that the stretching of taenia coli muscles cause depolarization in the muscle fibre [8,9]. She also wrote a book on the same subject (Smooth Muscle, an assessment of the current knowledge, 1981).She became a member of the British Pharmacological Society in 1936 and the Physiological Society in 1937. In 1949 she published a paper first showing that adrenaline was synthesized from noradrenaline by an ATP mediated methylation [10,11].One of her landmark publications came in 1946, in which she described the rat diaphragm preparation [12].

Gertrude Elion was a scientist with a master's degree in chemistry, who worked closely with George Hitchings on purines. At that time, the structure of DNA had not been elucidated. What was known was that nucleic acids were the building blocks of DNA. Even though she was trained as an organic chemist, it did not prevent her from widening her field of expertise into biochemistry, pharmacology and virology.

In the 1940's the antimetabolite theory was put forth (Woods and Fildes) explaining the action of sulfonamides. George Hitchings was of the opinion that if it was possible to arrest the growth of a bacterium with an antimetabolite like sulfonamides, something similar may be possible with antagonists of nucleic acids. It was thought that it might have some use in the treatment of cancer as well as in the treatment of microbial diseases [13]. After that, a search began for a substance that could antagonise the actions of nucleic acids. At this time, they needed a system or assay which could tell them that a particular drug was antagonising nucleic acids. This is where another woman scientist called **Elvira Falco** came into the picture [14, 15]. She developed an assay system based on *Lactobacillus casei*, which could grow in a mixture of thymine and a purine. It could also synthesize purines if provided with folic acid. Then the laborious task of actually subjecting the chemicals to this assay system and screening for antibacterial activity started. In 1948, Elion used this assay system to discover that 2-6-diamino purine inhibited the growth of *L casei* [16,17]. The drug was sent for testing on mouse tumors and tumor cell lines and it did indeed have antitumor activity but proved too toxic for use. The doorway had been opened for further research. Using her knowledge of organic chemistry, she produced 6-mercaptopurine (1950) and 6-thioguanine which paved the way for many more drugs to come (azathioprine, acyclovir, allopurinol). Since there were no drugs available at that time which could prolong survival in leukemic children, it was a major break though. Nowadays, azathioprine and 6-thioguanine are also used for their immunosuppressant properties. Elion and Hitchings were awarded the Nobel Prize in 1988.

In 1958, 6-mercaptopurine was used to prevent transplant rejection in a dog. Elion had modified 6-mercaptopurine into many compounds which were also checked for their immunosuppressant activity. In 1959, azathioprine was used successfully in a dog to prevent transplant rejection [18]. She also determined the mechanism of action of acyclovir which was developed earlier by Howard Schaeffer. Gertrude Elion hired **Janet Rideout**, an organic chemist to work with her at Burroughs Wellcome (Glaxo Smithkline). Elion died in 1999 whereas Janet walked the same path as her mentor and went on to make important contributions to pharmacology and medicine, the prominent among which is the patent for azidothymidine (AZT or zidovudine) which she shares with a few other scientists, two among them being women (**Sandra Lehrman**, infectious disease expert and **Martha St.Clair**, a virologist) [19].

The story of the discovery of penicillin has been told often. But what happened later is equally important since only after mass production was the true potential of the drug realised. Once the penicillin extracts had been successfully tried on mice by Florey and Chain, there was a need for knowing the exact structure of penicillin so that it could be manufactured on a large scale. But it was not to be till much later that this would be achieved. Meanwhile, the major problem faced by scientists was to extract enough penicillin to be clinically useful. Among the many scientists involved, **Gladys Hobby** (1910-1993), a bacteriologist was a prominent figure. She was a part of the team that synthesized penicillin first to test it in humans. Their first scientific paper to that effect was published in 1941. Pfizer got interested in the molecule and finally took over the production in 1941. Thereafter, she worked extensively with penicillin and wrote several papers on the same [20-22]. She recorded her experiences with penicillin in a book called 'Penicillin: meeting the challenge', which was published in 1985. Gladys Hobby joined Pfizer and later worked on streptomycin, oxytetracycline etc. She was also the founding editor of the journal Antimicrobials and Chemotherapy and has published numerous papers on antimicrobials and their development [23].

Another woman whose name is also associated with the mass production of penicillin is that of **Margaret .H. Rousseau**, a chemical engineer. She designed the first commercial penicillin production plant during the World War II. With their efforts, even though penicillin was being produced commercially, the exact structure was elucidated much later by Dorothy Hodgkin.

Dorothy Mary Crowfoot Hodgkin was educated at Oxford and chose chemistry as her subject. She attained expertise in X-ray crystallography which could be used to deduce the molecular structure of substances. She worked in Cambridge with J.D Bernal who had an interest in biological molecules. The first organic molecule to be analyzed was cholesterol iodide and this distinction was achieved by Dorothy Hodgkin with C.H Carlie.

Between 1942 and 1949 Dorothy Hodgkin worked on the structure of penicillin [24,25]. Her efforts were rewarded in 1945 when she discovered that penicillin consists of a beta lactam ring and a thiazolidine ring. This was achieved by crystallizing the penicillin molecule, bombarding it with X-rays and then deducing the molecular arrangement. For her work on penicillin, she was awarded a fellowship of the Royal Society in 1947.Once the structure of penicillin was elucidated, it paved the way for the production of the many synthetic penicillins. The structure described by Hodgkin was, in a way, a confirmation of a structure proposed earlier in the pre X-ray crystallization techniques era. She also described the structure of cephalosporins. But her major contribution was yet to come.

After 1948, Dorothy Hodgkin started working on the structure of vitamin B12. This research lasted almost a decade. She was awarded the Nobel Prize in 1964 for her work on vitamin B_{12}.

In 1969, she discovered the three dimensional structure of insulin. It took her almost 30 years for this, since analysis of the X-ray crystallographic data without the aid of computers involves a lot of complex mathematics. This illustrates the fact that nothing can be achieved without persistence and commitment to a cause with single minded devotion, irrespective of the hurdles that might be lying in wait.

Rosalyn Yalow was another woman who broke the trend and joined the University of Illinois in 1941.She was the only woman among 400 members and the only woman who had been admitted since 1917. She received a PhD in nuclear physics. She worked on the applications of radioisotopes in various aspects of medicine. Her most important contribution was the development of radioimmunoassay (RIA). In 1947, Yalow became associated with Veterans Administration Hospital in Bronx, where research was being carried out on medical applications of radioisotopes. This research was headed by Dr. Solomon Berson, who had earlier worked with Yalow to develop a method to quantify the amount of blood cleared of iodine by the thyroid gland per unit time (iodine uptake by thyroid gland). Yalow and Berson attached radioactive iodine to molecules of beef derived insulin and injected minute quantities of it into normal subjects as well as diabetics. They discovered that globulins bound radioactive insulin in insulin treated diabetics. This was a significant discovery that introduced the concept of insulin binding antibodies [26]. The concept was not accepted widely at the time since it was not known whether a relatively small molecule like insulin could evoke an immunological response. This technique proved to be the birth of radioimmunoassay (RIA) which is so widely used now. This discovery opened up newer aspects of immunology and diagnostics. Various adaptations of RIA are enzyme linked and fluorescent assay which form the backbone of diagnostics today. Rosalyn Yalow received the Nobel Prize in 1977 [27]. Berson had expired in 1972 before he could share the award.

Anybody who knows about drugs knows about the thalidomide tragedy. Lesser known is the fact that a newly recruited woman officer of the US FDA called **Frances Oldham Kelsey** was responsible for keeping the drug off the US market and thus preventing a large scale tragedy of the same magnitude as that seen in Germany and the rest of Europe [28]. Frances Oldham Kelsey, who had worked earlier on quinine, knew by her experience with it that certain drugs could have a different effect on the embryos than in the adults. She kept asking for more safety data on the drug from Richardson-Merrel Pharmaceuticals, even though the drug was sold over the counter in Germany, Europe, South America and Canada. In spite of great pressures from the industry and the fact that she had joined the FDA just a month back, she did not change her stand. The company wanted to launch the drug as early as possible. But by then, the adverse reports had started trickling in. By November 1961, a German pediatrician determined that thalidomide was responsible for the increasing number of deformities seen in children whose mothers had consumed the drug during pregnancy. The drug was pulled out of the market and the US FDA application was withdrawn. Thereafter, the authorities woke up to the fact that drug laws needed to be strengthened. In recognition of her efforts to avert such a huge disaster, she was awarded the highest honor that can be bestowed upon a US civilian (the medal for Distinguished Federal Civilian Service).

Apart from being associated with thalidomide, Kelsey Oldham's name is also associated with sulphanilamide, during her PhD program. Sulfanilamide (1935), though an effective antibacterial agent, was unpalatable. In order to mask the taste and make it acceptable to children, the manufacturers added certain excepients and sold the drug. Reports of deaths started coming in and it was evident that they were due to the new drug formulation. Kelsey helped conduct animal studies to isolate the toxic substance, which, incidentally was diethyl glycol. Diethyl glycol was the solvent used to make the solution of sulphanilamide. But by then it was too late. About 107 deaths had already occurred. This earlier experience probably shaped her attitudes to viewing new drugs with scepticism till their safety had also been proven along with their efficacy.

Martha Vaughan is another scientist held in high esteem in the field of pharmacology. She has worked extensively in pharmacology at the molecular level andhas elaborated on various aspects of metabolism [29,30]. She was felicitated by NIH in 2001. Ground breaking work was carried out in her laboratory. The likes of Ferid Murad (Nobel Prize winner 1988) worked under her guidance. She researched the role of G-proteins and cyclic nucleotides. Her work has contributed a lot to the understanding of intracellular signalling. Currently her research involves ARF (ADP-ribosylation factor), GTPase and mechanisms of their signalling and regulatory functions.

Other women scientists worthy of special reference are:

Anne-Marie Staub (H1 blockers)

Mary Pickford (ADH)

Gerty Cori (glucose metabolism)

Rita Levi Montalcini (rabies vaccine)

Rosalind Venetia Pitt-Rivers. Thyroid hormone (triiodothyronine)

The lives and achievements of these women in science underline the fact that genius cannot be suppressed. If there is a will, then obstacles just turn into stepping stones. The scene has now changed somewhat. Whereas it is no longer difficult for women to enter scientific fields, the fine tuned balance between professional life and family commitments is not easy to achieve. Statistics from the British Pharmacological Society (BPS) reveal that only 28% of the members are women, which is surprising, since 63% of undergraduate students studying pharmacology are female [31]. At postgraduate level in pharmacology, 64% students were female. Out of these, only 10.2% moved to professional level. This mid-career attrition has been attributed to various factors like family responsibilities, lack of flexible timings, high cost of child care etc. The fact remains that women are finding it difficult to divide time between work and family. The increasing trend of nuclear families is also bound to have a negative impact on the female scientific community. In a world where a drug discovered yesterday becomes obsolete tomorrow, to keep pace with drug development after time off due to child bearing and rearing can be a daunting task. It is to be hoped that things might change in favor of women scientists in future.

REFERENCES

1. Cuthbert A W. A brief history of the British Pharmacological Society. *British Journal of Pharmacology* 2006; 147, S2–S8.
2. Bell.C. Marthe Louise Vogt. (1903-2003). Downloaded from the e journal of British Pharmacological Society. pA2online accessed on 20.7.08 http://www.pa2online.org/articles/article.jsp?volume=5&issue=4&article=20
3. Dale HH, Feldberg W, Vogt M. Release of acetylcholine at voluntary motor nerve endings. *J Physiol* 1936; 86:318-341.
4. Vogt M. The output of cortical hormones by the mammalian suprarenal. *J Physiol* 1943; 102:341-356.
5. Vogt M. Cortical secretion of the isolated perfused adrenal. *J Physiol* 1951; 113:129-156.
6. Vogt M. The concentration of sympathin in different parts of the central nervous system under normal conditions and after administration of drugs. *J Physiol* 1954; 123:451-481.
7. Bolton TB, Brading AF. Edith Bulbring. 27 Dec 1903 - 5 July 1990. Bibliographical Memoirs of Fellows of Royal Society 1992; 38:68-95.
8. Bulbring E, Hooton IN. Smooth muscle potentials recorded with intracellular electrodes. *J Physiol* 1953; 120: 8p-9p.
9. Bulbring E. Smooth muscle potentials recorded in the taenia coli of the guinea pig. *J Physiol* 1954; 123: 55p-56p.
10. Bulbring E.The methylation of noradrenaline by minced suprarenal tissue. *Brit J Pharmacol* 1949; 4:234-244.
11. Bulbring E, Burn JH. Formulation of adrenaline from noradrenaline in the perfused suprarenal gland. *Brit J Pharmacol* 1949; 4:245-247.
12. Bulbring E. Observations on the isolated phrenic nerve diaphragm preparations of the rat. *Brit J Pharmacol* 1946; 1:38-61.
13. Rubin R.P. A brief history of great discoveries in pharmacology: In celebration of the centennial anniversary of the founding of the American Society of Pharmacology and Experimental Therapeutics. *Pharmacol Rev* 2007; 59:289–359.
14. Hitchings GH, Falco EA, Sherwood MD. The effects of pyrmidines on the growth of Lactobacillus casei. Science 1945; 102:251–252.
15. Hitchings GH, Elion GB, Falco EA, Russell PB, VanderWerff H. Studies on analogs of purines and pyrimidines. *Ann N Y Acad Sci* 1950; 52:1318–1335.
16. Elion GB, Hitchings GH. Antagonists of nucleic acid derivatives.IV. Reversal studies with 2-aminopurine and 2,6-diaminopurine. *J Biol Chem* 1950; 187:511–522.
17. Elion GB. The purine path to chemotherapy, in Nobel Lectures. Physiology or Medicine, 1981–1990 (Frängsmyr T and Lindsten J eds) pp 447–468, World Scientific Publishing Co., Singapore.
18. Jewish Women's Archive. "JWA- Gertrude Elion.- Transplants and antivirals" http://jwa.org/exhibits/wov/elion/trans.html
19. Vare EA and Ptacek G. Patently Female. Published by John Wiley, 2002. Page 93-94.
20. Meyer K, Chaffee E, Hobby GL, Dawson MH, Fleisher G. On penicillin. Science1942; 96:20-21.
21. Hobby GL.the antibacterial action of penicillin against Gram negative organisms. *Science* 1944; 100:500-501.
22. Hobby GL,Lenert TF, Reed W, Rinne D. The enhancement of the chemotherapeutic action of penicillin. *J Bacteriol* 1949; 57:247-252.
23. Hobby GL. The current status of the development of antimicrobial agents. Presented at the 27th graduate fortnight of the New York Academy of Medicine, 1954. *Bull N Y Acad Med* 1995; 31:181-197.
24. National Cataloguing Unit for the archives of contemporary scientists. The papers of Dorothy Mary Crowfoot Hodgkin. *Acta Cryst* 1996; D52:423-424.
25. Remembering Dorothy Hodgkin- a personal reminiscence on the British Crystallographic Association's Web site, reprinted from the American Crystallographic Association's Fall 1995 newsletter.
26. Berson SA, Yalow RS, Bauman A, Rothschild MA, Newerly K. Insulin I^{131}metabolism in human subjects:demonstration of insulin binding globulin in the circulation of insulin treated subjects. *J Clin Invest* 1956; 35:170-190.
27. Radioimmunoassay: a probe for the fine structure of biological systems. Nobel Prize lecture. *Science* 1978; 200:1236.
28. Bren L. Frances Oldham Kelsey: FDA medical reviewer leaves her mark on history. FDA Consumer magazine.March-April 2001.

29. Vaughan M. Effect of hormones on glucose metabolism in adipose tissue. *J BiolChem* 1961; 236:2196-2199.

30. Vaughan M, Berger JE, Steinberg D. Hormone sensitive lipase and monoglyceride lipase activities in adipose tissue. *J Biol Chem* 1964; 239:401-409.

31. Ahluwalia A. From the University of Cambridge, Summer 2005 Meeting: Proceedings of the British Pharmacological Society at http://www.pa2online.org/articles/article.jsp?volume=3&issue=11&article=44

CURRENT AUTHOR ADDRESSE

Neeta Dhar Grover, Department Of Pharmacology, Bharati Vidyapeeth Deemed University Medical College, Sangli. E-mail: neetadhargrover@hotmail.com