

Review Article

Folic Acid Therapy Completes 9 Decades — Originated in India

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The role of folic acid in the prevention of congenital anomalies in the new born is known to all Doctors since the last 93 years. However, what is perhaps not known is that the subject is very closely connected to India.

Two of the pioneers responsible for the scientific discovery of folic acid – Dr. Lucy Wills, an English physician and Dr. Yellapragada Subbarao of Andhra Pradesh were almost contemporaries and global citizens who worked in various parts of the world.

Dr. Wills conducted clinical research work on macrocytic anaemia of pregnancy in the late 1920's in the slums of Mumbai. She called it "Pernicious anaemia of pregnancy". Her article was published in the British Medical Journal way back in 1931.

Dr. Subbarao was the second scientist from India who further contributed to this subject. He developed a method to synthesize folic acid and Vitamin B9. He is credited with initial Research on Folic Acid antagonists and tetracyclines.

There after the progress in folic acid was rapid with contributions from many Researchers : Bryan Hibbert in 1964, Chanarin in 1969, Richard Smithells in 1983, Scott & Weir in 1995, 1970 - Ultrasound revolutionised the diagnosis of early birth defects.

This presentation will chronicle the life histories of Dr. Lucy Wills of UK and Dr. Yellapragada Subbarao of India who played a monumental role in the understanding of the role of folic acid in health and disease. The authors have also reviewed the recent developments in the synthesis of folic acid.

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The role of folic acid in the prevention of congenital anomalies in the new born and the associated foetal wastage is well known to all the Obstetricians. Further all Doctors & Physicians know that it is used in the prevention & treatment of Megaloblastic Anaemia. However, what is perhaps not known is that this subject is very closely connected to India. Two of the pioneers who were responsible for the scientific discovery have a connection with India. We should take pride in this and let the new generation of Indian Doctors be inspired by their life and works.

This presentation will chronicle the life histories of Dr Lucy Wills¹ of UK & Dr Yellapragada Subbarao² of India who played a monumental role in the understanding of the role of folic acid in health & disease. The authors have also reviewed the recent developments in the synthesis of folic acid.

Dr Lucy Wills, an English lady Doctor, worked in Mumbai at Haffkine Institute from 1928 to 1933. Dr Yellapragada Subbarao was born in Andhra Pradesh. They were almost contemporaries and were born in 1888 and 1895 respectively. They were both global citizens and worked in various parts of the world including India. It is not known whether they ever met or communicated with each other. However, both have left an unforgettable stamp on the story of folic acid and pregnancy.

The First Most Important Indian Connection is Dr Lucy Wills :

Dr. Lucy Wills was born in 1898 into a learned family which lived in Birmingham area³. She studied at Cheltenham College for

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Editor's Comment :

- Periconceptional supplementation of folic acid is recommended for all pregnant women.
- Whenever Medical discoveries made by Indian Doctors, or have occurred in India, it is important to ensure that Indian doctors are aware of it.
- There is a continual Research going on even in a simple drug like FOLIC ACID. All doctors need to be informed.
- Improvements in the health of pregnant women will ensure Good Health of Future Generations.

girls and was known as a brilliant student.

Dr Lucy Wills was encouraged by her family to become a Doctor. In that era, opportunities for women to enter Medical profession were few. The London School of Medicine for Women was established in 1874 and had the distinction of being the first Medical School in England to enrol women³.

In January 1915, she joined the London University as a Medical Student. She graduated in May 1920 with a degree of LRCP (Licentiate of the Royal College of Physicians). In December same year, she was conferred MBBS (Medical Bachelor and Bachelor of Science) from London University.

There were a few Indian Students at the Royal Free Hospital & there were some academic interactions with India. One of the well-known & well-respected students was Dr Jerusha Jhirad⁴ who graduated with a degree in Obstetrics and Gynaecology in 1919, the year before Lucy Wills graduated.

On qualifying, Lucy Wills took a surprising decision not to practice as a physician, but to teach and do research. She decided to go to India and arrived in Mumbai. She joined Haffkine Institute as a Researcher in 1928.

Dr Margaret Balfour of the Indian Medical Service had asked her to join the Maternal Mortality Enquiry sponsored by the Indian Research Fund Association⁴ at the Haffkine Institute in Bombay

(now Mumbai). The Lady Tata Foundation also provided financial support.

Lucy Wills was in India between 1928 and 1933, mostly based at the Haffkine Institute in Bombay. She conducted Clinical Research work in India on Macrocytic Anaemia of Pregnancy⁵.

She saw many pregnant young women with classical Macrocytic Anaemia who were working in the cotton mills. It was identical to Pernicious Anaemia described earlier. However, that anaemia occurred in the elderly, was progressive and sometimes fatal. The anaemia she encountered was limited to pregnancy and there was spontaneous cure after delivery. Therefore, she called it Pernicious Anaemia of Pregnancy.

Dr. Lucy Wills found some striking differences in the anaemia in Mill workers, who had poor nutritional status from true pernicious anaemia⁵. Her patients did not have deficiency of gastric acid in the stomach known as achlorhydria. True pernicious anaemia patients responded to "pure" liver extracts (Vitamin B12) whereas her patients responded only to "crude" liver extract. She came to the conclusion that there must be another nutritional factor other than Vitamin B12 deficiency. For many years this was known as the "Wills factor". It was only in 1940 that it was discovered that this was a "natural folate" which was found in yeast extracts & a supplement called "Marmite". Much later it was found that "Natural Folate" was a precursor of synthetic Folic Acid.

Her article entitled "Treatment of Pernicious Anaemia of Pregnancy and Tropical Anaemia" with special reference to yeast extract as curative agent was published in the British Medical journal way back in 1931⁶.

Dr. Wills report was based on clinical observations and she treated her patients with a yeast extract called "Marmite" which was a rich source of folates. Hence, she is credited with the discovery of "folates" in the treatment of anaemia in pregnant women.

Dr. Wills was keen to do further Research. She was able to get an opportunity to work in world famous Pasteur Institute which was in Coonoor in The Nilgiris. In the year 1929, she moved to Coonoor. Luckily Sir Robert McCarrison was the Director of Nutrition & he was very supportive. She was able to work with Indian Researchers, so was able to publish 2 Scientific papers on her experiments on Albino Rats^{7,8}.

She undertook experimental work on dietary manipulations on Albino Rats. Rats when fed on diet similar to the Muslim women working in the Mills developed this type of anaemia & some of them even died during pregnancy. This anaemia could be prevented by nutritional supplement of yeast extract without the addition of Vitamin B12. Later she repeated these experiments on Macaque monkeys.

After Coonoor, she returned back to Bombay & carried on with the Clinical Research proving that megaloblastic anaemia of pregnancy could be prevented & treated with yeast extract⁹.

She returned to UK to work at Royal Free Hospital during the summer months. In 1933, she went back as a full time Pathologist at Royal Free but still was able to come back to Haffkine Institute & continue her Research. In early January 1938, for the first time, Lucy Wills travelled by air to Karachi and onwards by sea⁹.

Before retiring from Royal Free Hospital, she set up a full-fledged Haematology Department. In 1947, she retired after a long & distinguishing career. During her lifetime, she travelled extensively to South Africa, Fiji & Jamaica continuing her interest in the subject.

Lucy Wills proved that hard & sincere Research work brings lasting benefits to Mankind. Ever after retirement she continued to stay in touch with people & Institute, she served all her life. Her virtues were recognised by her colleagues & she received much honour, respect & adulation from them.

Her last few years she spent with her lifelong friend Margot Hume in a Cottage in Surrey where they nurtured a Botanical Garden.

When she passed away on 26th April 1964, she was deeply mourned by many friends from all over the world¹⁰.

The Second Most Important Indian Contributor is Dr Yellapragada Subbarao :

Dr Subbarao developed a method to synthesise folic acid and vitamin B9. His work on synthesising Folic Acid to treat megaloblastic anaemia followed that of Lucy Wills earlier work¹¹. He did this while he was appointed at Lederle laboratories, a division of American Cyanamid. It is now a division of Wyeth Ltd. which has recently merged with Pfizer Ltd.

Dr Y Subbarao was born on 12/1/1895 in a village in Andhra Pradesh. He had a difficult childhood but was known for being a bright student. He entered Madras Medical College. His father in law supported his education. Those were turbulent years of Indian National Congress and freedom struggle. He started wearing khadi clothes and took interest in Indian Systems of Medicine¹². He was encouraged to go to USA by his friends and well-wishers for further education. He joined Harvard. He did monumental work in the role of ATP (adenosine triphosphate) in muscular activity and obtained a PhD.

On joining Lederle Laboratories, in addition to folic acid he worked on methotrexate along with Dr. Sidney Farber. He also discovered Hetrazan which WHO used against filariasis in World War II. Aureomycin, world's first tetracycline was developed by him in 1945 with Benjamin Duggar.

His journey into the development of cancer chemotherapy was a logical sequence of his knowledge of folic acid and then the role of folic acid antagonists.

Through all the professional successes he achieved, he remained a very simple man, a staunch vegetarian and a private person. His achievements should have been enough to guarantee him a professorship at Harvard so says Mukherjee in "Emperor of all Maladies"¹³. Tribute was also paid to him by his colleague George Hitchings who shared the 1988 Nobel Prize in Physiology with Gertrude Elion. Many believed that he too, should have been included among the group who received the 1988, Nobel prize¹⁴.

The only lasting tribute was paid by American Cyanamid who named a fungus "SUBBAROMYCES SPLENDUS" in his honour.

Writing in the April 1950 issue of ARGOSY, D K Antrim observed "you've probably never heard of Dr. Yellapragada Subbarao. Yet

because he lived, you may be alive and are well today. Because he lived, you may live longer"¹⁴.

He died at the young age of 53 years in New York on 9th august 1948. But he lived long enough to see his beloved India gain independence. Till the end he maintained his Indian passport and did not seek a green card though unhesitatingly he contributed to some of America's most important Medical Research during World War II.

Conclusion:

It took another quarter of a century for further progress in the use of folic acid in pregnancy. It was Bryan Hibbard¹⁵ in 1964 who reported the importance of folates in the embryonic development.

Chanarin¹⁶ in 1979 explained the genesis of megaloblastic anaemia. Another important research was the work of Richard Smithells¹⁷ in 1980 when he stated that the early birth defects could be prevented by the use of folic acid. This applied especially to neural tube defects. It was only in 1995 that Daly, Scott and Weir categorically showed that folic acid therapy prevents Neural Tube defects^{18,19}.

Fortunately, today in the 21st century, ultrasound can pick up neural tube defects in early pregnancy and in most countries termination of pregnancy is permitted. However, it is a great personal tragedy for the parents. What is needed is awareness and education of the public that peri-conceptional therapy with folic acid is required to prevent this foetal wastage. There are some countries where fortification of food is done with folic acid as a preventive measure.

Progress has continued in the 21st Century. Newer formulations of Folic Acid have been introduced in practice.

The understanding of several enzymatic processes has unravelled the role of a biologically active L-Methyl Folate²⁰. It can overcome the deficiency of MTHFR which is a genetic polymorphism.

Further L-Methyl Folate if combined with DOCOSA-HEXAENOIC ACID (DHA)²¹ improves brain & eye development in the 3rd trimester of pregnancy. Hence this combination is highly recommended from 24th week of gestation to lactation period to ensure maximum brain development in the foetus.

We can look forwards to further developments in the Story of Folic Acid in promoting Health of Future Generations.

So, we hope that when all the Medical Practitioners who write prescriptions of folic acid will at that moment feel proud of the fact that India has made a significant contribution to the knowledge of this great product which has saved so many lives.

We would also like to reiterate that Science knows no boundaries,

neither geographic nor racial. Finally, Research is a never-ending ongoing process which brings much benefit to Mankind.

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