Yellapragada SubbaRow – The unsung Indian biochemist behind methotrexate and other drugs

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"You have probably never heard of Dr. Yellapragada SubbaRow. Yet because he lived you may be alive and well today, because he lived you may live longer." wrote Doron K. Antrim in "Argozy," an American magazine in 1950s.[1] Methotrexate has been proved to be one of the best United States Food and Drug administration-approved drugs for dermatologists in India, as it is cheap and effective in managing cases of psoriasis and Sezary syndrome along with many off label uses.[2] Most of the clinicians in an overpopulated country like India have prescribed methotrexate, while being ignorant of the brain behind the molecule.

The person who discovered this molecule had some of the greatest contributions in more than one basic field of science, i.e., biochemistry, pharmacology, microbiology, oncology, and nutritional science, and these continue to be applied to numerous experiments which are relevant to science even today.[3] His article titled "The colorimetric determination of phosphorus" published in the Journal of Biological Chemistry has been one of the most frequently cited (>21,000 citations) articles in the world and still is unknown to most in the Indian medical fraternity.[4] So, let us relish the achievements of this Indian genius of organic chemistry by recounting the story of his life.

Yellapragada SubbaRow [Figure 1] was born on 12th of January, 1895 in a Telugu Brahmin family, in the West Godavari district of Andhra Pradesh. He entered the Madras Medical College for medical education with a vow that he had made to his mother: "I must win a name in the world, and then only would life be worthwhile."[5] He started wearing khadi gown to his medical college, following Mahatma Gandhi's call for boycott of British goods during the non-cooperation movement in August, 1920. This incurred the displeasure of his surgery professor M. C. Bradfield and though he did well in examinations, he was awarded the lesser Licentiate of Medicine and Surgery certificate instead of an MBBS degree. He thus failed to enter the Madras Medical Services and had to take up the job of lecturer in anatomy and physiology at the Madras Ayurvedic College.[3,5]

His teaching methods and work ethics impressed Dr. Lakshmi Pathi, who was the then principal of Ayurvedic College, and he promoted SubbaRow to the post of Vice Principal.[5] He was encouraged by a visiting American Doctor, John Fox Kendrick, to go to Harvard School of Tropical Medicine. With help of a loan from his father-in-law and an annual scholarship of Rs. 1500 for three years from the MSN charities he joined the Harvard School of Tropical Medicine, Boston, USA for post-graduation in Tropical Medicine. Here, his LMS degree did not qualify him to get a scholarship or an internship and so he supported himself by working as night porter cleaning urinals and bedpans of patients and doing other odd jobs in spare time.[6]

After earning a diploma from the Harvard University School of Tropical Medicine in June, 1924, he managed to join Harvard Medical School. Here, Professor Otto Folin assigned SubbaRow to Dr. Cyrus Fiske, who had been assigned the task for accurate measurement of phosphorous in cell, nerve, and bone tissue. Fiske who was a diligent researcher and a hard taskmaster, was difficult to please. SubbaRow began working in his biochemistry laboratory where they developed the Fiske–SubbaRow method for the estimation of phosphorus in body fluids and tissues. SubbaRow over the years developed a friendly relationship with Fiske along with a sense of loyalty towards his guide and mentor, which he never regretted.[5] His discovery of the role of phosphocreatine[7] and adenosine triphosphate[8] (ATP) in muscular activity earned him an entry into biochemistry textbooks. His discovery and publications on the Fiske–SubbaRow method of phosphorous estimation paid off and he was awarded his Ph.D. degree in June, 1929, at Harvard Commencement Program.[8]

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Figure 1: Yellapragada SubbaRow (http://www.ysubbarow.info/Archive/admin_login/uploaded_files/gallery/big/a834808fe4621f311f10d34af26dd6d3.jpg) - Courtesy of the Yellapragada SubbaRow Archives Online

His journey towards liver extract fractionation and isolation of factors which can cure pernicious anemia started in 1927. His charm attracted a number of pharmaceutical companies like Merck and Lederle laboratories, which were desperately looking for top scientists to work in vitamin research. After he was denied a regular faculty position at Harvard, Lederle promised him the necessary support along with the post of Director of Research at their plant in Pearl River, New York. Thus, he decided to join an institution that shared his enthusiasm to conquer diseases. The amusing condition he put forward was that instead of $14,000 annual salary offered, he would accept half if a new research building was constructed for him at Pearl River. SubbaRow later said to William Berenberg that he was not concerned about the finances for personal benefits but more for a chance to work at a modern research facility, without having to be concerned about budgets.[3,5]

Along with Fiske and Jacobson he was able to isolate the anti-pernicious anemia factor (now known as vitamin B12), niacin and its therapeutic effects in pellagra, pantothenic acid (vitamin B5) and biotin.[9–11] Along with Dr. Robert Angier, N. Bohonos, James Boothe, Brian Hutchings and a few others, he successfully developed a method to isolate and synthesize folic acid (vitamin B_9) on industrial scale which contributed further to the profits of Lederle.[12] After the 1941 attack on Pearl Harbour, when the U.S. Army got involved in the Pacific wars in the tropics of south east Asia, SubbaRow initiated a new project to protect the soldiers by including "parasiticides" in his research agenda. His work was directed towards development of an orally administrable non-metallic drug, which led to the discovery of diethylcarbamazine, a piperazine compound, which has been recognized by the World Health Organization as a principal element for prophylaxis and treatment of filariasis.[13]

When the Indian freedom struggle intensified in 1945, his personal conquest began in direction of cancer treatment, especially after Dr. Richard Lewisohn in 1944 published reports of folic acid having inhibitory effect on cancer cells.[5] While working with Dr. Sidney Farber, the father of modern chemotherapy, he developed an effective folic acid antagonist drug named aminopterin – one of the very first cancer chemotherapy agents used by Farber in children suffering from acute leukemia.[6] In 1947, folic acid antagonist teropterin and aminopterin were found to be effective in acute leukemia cases but were also equally destructive for normal cells of the body. Moreover, long-term studies showed relapse of leukemia in all patients exhibiting a temporary control at a high cost of adverse effects.[14] One of his internal memos showed how he directed his team to put efforts in producing a relatively nontoxic compound that would lead to discovery of amethopterin or methotrexate, which was much safer.[5] In 1948, Farber in his seminal article published in New England Journal of Medicine, acknowledged SubbaRow and his team's contribution as a foundation for their landmark paper.[14]

In 1941, he recruited into his team a retired professor of mycology, Prof. Benjamin Duggar, as a consultant in mycology research for discovering newer antibiotics, and then went on to discover polymixin in 1945.[5] SubbaRow took a backseat in the Roosevelt Memorial, when Duggar introduced the world's first tetracycline antibiotic, aureomycin, at a function organized by the New York Academy of Sciences.[15] Aureomycin was his last gift to the mankind, as he left the world on the 9th of August, 1948, only a fortnight after the New York Conference, at the age of 53 years.[5]

After Farber and SubbaRow presented evidence of success of methotrexate in leukemia, Dr. Richard Gubner of New York College of Medicine along with some physicians from the Kings County Hospital carried out a clinical trial of aminopterin in psoriasis, proving that it was a potent inhibitor of connective tissue proliferation and effective in psoriasis.[16]

In 1953, Clifford Hesseltine, who had witnessed the enthusiasm of SubbaRow in his work, discovered a new species of fungus in Pearl River and named it after him as Subbaromyces splendens.[5]

SubbaRow never pursued fame, maybe because of his disinterest in marketing himself and his reluctance to step into the limelight. He never seemed to be interested in giving interviews to the press or taking rounds of the academies or go on lecture tours.[10] In his biography, Dr. S.P.K. Gupta rightly says: "He was quite determined that the time allotted to him on earth should be completely devoted to finding cures for ailments that plagued mankind."

His efforts always seemed to be more focussed on research than acquiring credit for it and his humble nature of sharing credit with his junior researchers, who worked devotedly under his guidance, was indeed a rare quality. The most enlightening thing about his life was the amount of energy and enthusiasm he put selflessly in efforts for scientific research and his devotion to medicine.

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