Dr. Yellapragada SubbaRow (1895-1948)
He Transformed Science; Changed Lives

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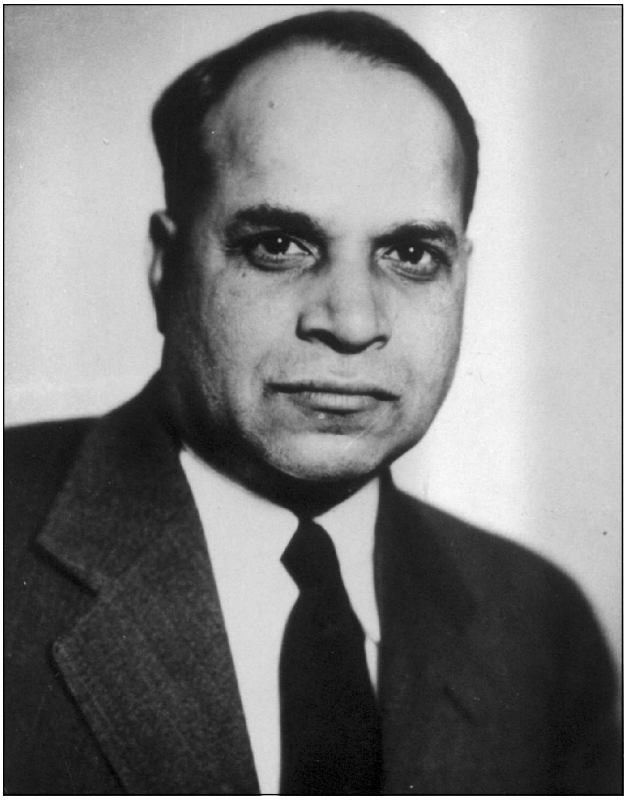

Most of the famous scientists around the world are known only for one major discovery that has had a lasting impact on our lives : Wilhelm Roentgen for x-rays, Marie Curie for radium, C V Raman for the scattering of light by liquids, P M S Blackett for cosmic rays, Ronald Ross for the life cycle of the malarial parasite, Alexander Fleming for penicillin – all awarded the Nobel Prize for their one major discovery.

There have been a few scientists known for two discoveries : Albert Einstein for the photoelectric effect and the theory of relativity, John Bardeen for transistors and super-conductivity, Hargobind Khurana for the genetic code and synthesis of gene.

Occasionally a scientist makes a large number of discoveries albeit in only one field like Robert Woodward in organic chemistry.

Then there are persons who have made important contributions but have not received the Nobel Prize or equivalent honours like Jonas Salk who made the first polio vaccine, Michael Heidelberger the father of modern immunology, G N Ramachandran who discovered the structure of collagen, the most abundant protein in our body and also laid the foundations for CT scan and NMR technologies.

Rarely, extremely rarely, a person comes on the world scene and transforms science and our lives by making a large number of major discoveries in – and otherwise makes important contributions to – more than one basic field and does not only not get a Nobel Prize but does not get to be known by name to most people, including scientists around the world.

I am referring to Yellapragada SubbaRow. Such an individual is perhaps born once in a thousand years or more. I do not believe there is any other person in the documented history of biology and medicine over the last 5,000 years who made such a large number of basic discoveries that are applied so widely.

SubbaRow was born in India in 1895 and he died in USA in 1948 at the young age of 53.

He went to the United States in 1923 after graduating from the Madras Medical College and worked at Harvard Medical School until 1940 when he went to Lederle Laboratories to direct its medical research.

The search he directed at Lederle Laboratories for antibiotics with wider range of cures than the then available penicillin and streptomycin led to the discovery of polymyxin widely used even today in cattle-feed and aureomycin the first of tetracycline

antibiotics which all of us have had some time or the other in our lives. Tetracyclines have saved millions of lives over the last 50 years.

Aureomycin was presented to medicine in 1948, the year SubbaRow died. It was the first broad-spectrum antibiotic, that is, one effective against both gram-positive and gram-negative germs. It was thus more powerful than either Fleming's penicillin or Waksman's streptomycin.

When SubbaRow's centenary year began in 1994, tetracyclines – especially doxycycline – helped confine and then eradicate the plague epidemic that broke out in Gujarat and Maharashtra. It was a debt SubbaRow paid to his motherland almost half a century after death which claimed him soon after the unveiling of Aureomycin before a medical gathering at the New York Academy of Sciences.

Doxycycline, the third generation tetracycline, has recently been cleared as a malaria preventive. The international staff of the United Nations Assistance Mission in East Timor (UNMET) packed it in their survival kits when ordered last year into the region wrested from Indonesia.

SubbaRow and his team of organic and biological chemists isolated folic acid from liver and a microbial source and then synthesized it in 1945.

By the clinical trials he organised, SubbaRow had the satisfaction of knowing that it cures tropical sprue which took him to the death's door while a medical student in Chennai and carried away two of his brothers. It was subsequently found to cure a variety of anaemias. The US government has since January 1, 1988 required that all flour, pasta and other grain products be enriched with folic acid to stave off spinal-cord defects in newborns. In mid-1999 the New England Journal of Medicine reported that this has already reduced levels of homocysteine, an amino acid, among the US population. Homocysteine is a risk factor in coronary heart diseases. Therefore that report has started a debate whether folic acid can control a significant cause of heart diseases.

It is a pity SubbaRow is not given the credit for laying the foundations for the isolation of Vitamin B_{12} the antipernicious anaemia factor. Our daily requirement of B_{12} is just one microgram. That is all you require, but it is extremely important you get it. If you have those indescribable pains all over, chances are that you need it. SubbaRow spent years trying to isolate it from liver and succeeded, but failed to recognise it. Others opened the door he found.

In 1965 or 1966, I met Sir Alexander Haddow, a very distinguished and handsome scientist. He was then the director of the Chester Beatty Cancer Research Institute in London. We started talking about methotrexate which was being used widely not for curing but alleviating the suffering from Burkitt's lymphoma, one kind of cancer, and he said, "Do you know that methotrexate was discovered by an Indian?" You can imagine the sense of pride I felt.

SubbaRow got aminopterin, which reverses the action of folic acid, synthesized when reports of a clinical collaborator indicated that chemicals resembling the vitamin arrest the growth of cancer cells. He thus initiated the chemotherapeutic approach to the treatment of cancer. Methotrexate, a derivative of aminopterin, has since then been the drug of choice in childhood leukaemia and many adult cancers. Subsequently, methotrexate has been used by doctors to control rheumatoid arthritis and psoriasis. More recently, it has been employed for medical abortion and in ectopic pregnancy and Crohn's colitis. Now comes a report in Chest that low-dose methotrexate spares steroid usage in asthma patients. There seems to be no end to such new SubbaRow miracles!

As Director of Research at Lederle, SubbaRow established a project for protecting American soldiers fighting in the Pacific from malaria and filariasis. He found in *Hetrazan* the cure for filariasis. It is today the most widely used drug against filariasis which leads to the deformity-causing elephantiasis. For years there was hesitation in employing diethylcarbamazine (DEC), the generic name for *Hetrazan*, in mass

campaigns against the scourge of elephantiasis because of certain unpleasant side effects like nausea. The World Health Organisation (WHO) has found that these side effects were due to unnecessarily high dosages previously prescribed and that it was enough to administer only a single dose of DEC, concurrently with invermectin, to keep blood free of filarial worms for a whole year. And WHO has made DEC a key element of its worldwide campaign for the elimination of elephantiasis.

Let me go backwards in time. When I raise my hand I am consuming energy. We derive energy from the food we take. A good part of what we eat is converted by the body into glucose. A mechanism in the body metabolises glucose and in the process generates energy the muscles use for running, raising hands, and doing the work of everyday life. That alone wouldn't be enough. There must be ways of storing the energy obtained from food because we are not eating food all the time. There was a hunt therefore in the 1920s for the chemical substances in the body acting as energy stores on which the body draws whenever it needs energy. It was SubbaRow who co-discovered, while working with Cyrus Fiske at Harvard, the two chemicals – phosphocreatine and adenosine triphosphate (ATP) - that store energy in our body. In fact, all living organisms store phosphocreatine as their source of energy. When the body needs energy, ATP is converted into ADP (adenosine diphosphate) and ATP is replenished by phosphocreatine while the body rests.

Not only did he show how important phosphorus is for our body, SubbaRow also devised the perfect way of estimating phosphorus in living organisms. There may not be any biologist of any kind anywhere in the world who has not some time or the other used the Fiske-SubbaRow Method of estimating phosphorus. In all fairness it should have been called the SubbaRow-Fiske method but SubbaRow put the name of his supervisor first on the paper describing it.

Trained first as a mathematician and physicist and then as a chemist with no formal training in biology, I got introduced to experimental biology through estimating phosphorus. And I used the Fiske-SubbaRow Method. That was in 1953. Hailing from Andhra as I did, I remember asking how he spelt his name Row and not Rao. As I learnt later he would have been the last man ever to cause a row! If you look at citations of scientific papers - which is the way others use your scientific work and quote it in their publications - SubbaRow turns out to be one of the most highly cited scientists in the entire history of science.

Thus far about his work. What about the man himself? I have a wish list of ten persons from the beginning of human history I would have liked to meet personally. In it figures SubbaRow along with Chanakya, Ashoka, Leonardo da Vinci. I regret I never knew him. My first visit to USA was five years after he died but I have met and talked about SubbaRow with people who knew him intimately.

What came through in these talks, apart from his scientific brilliance, was his tremendous modesty and self-effacement. This was very difficult to understand as he was driven by a desire to be famous. But he was at the same time generous in giving credit for what he had done to someone who stood to gain a great deal thereby. It is difficult to reconcile these two qualities but all of us have a little bit of such contradictions in us.

Fiske would not have got the position he did at Harvard but for SubbaRow sharing with him the credit for the method of estimating phosphorus in biological fluids. My friend, S P K Gupta, in his biography of SubbaRow has documented many such acts of his to get a friend or a colleague get a promotion or a job or an advantage.

SubbaRow's cultural pluralism is another thing that comes through in his documented life and work and in personal dialogues with people who knew him. He had this multiplicity of backgrounds which intermeshed in his personality: He was extremely Indian and identified himself as an Indian. He was conversant with our ancient scriptures and his early work was in Ayurveda. But he also provided

financial support to the Church, especially to churches which seemed to have an universal element in their beliefs and to their education programmes. It is strange that while he was an Indian in reality always, an Indian visiting him in USA told his family in India that SubbaRow had become totally Americanised. Appearances can be deceptive!

We must give credit to the United States for giving him the kinds of facilities to work not previously given to any Indian. But there is another side to the story that must be told. Let me quote from the biography, *In Quest of Panacea*, some bits that show how politics operate in the world:

"SubbaRow's admission to the U.S. and his stay there for a quarter of a century was possible because he went there as 'a physician' and qualified himself as a 'chemist' – two of the professions that were exempt from the ban on immigration of Indians in force from 1917."

The Supreme Court ruled that Hindus were not Caucasians and the President excluded from American citizenship even those Indians who had been legal immigrants and had met the minimum residence requirement.

"Although he could get his 'student' visa, originally valid for two years, periodically extended because he belonged to the excepted category, 'he was always mortally afraid ... that he might be picked up for some minor infraction of the law and be shipped back to India... Then came the Second World War and the Alien Registration Act of 1940. SubbaRow had always to carry from then on a card bearing his right thumb impression, signature and registered number (3420564) testifying to his status as an 'alien', one of the 3896 East indians on the Registry. And he had to report his address every three months to the Department of Justice in Washington.

"In 1942, he had to get special clearance because his position as Director of Research at Lederle was considered sensitive in view of his supervision of the processing of blood albumin for supply to the Navy and of the research on tetanus and gas gangrene toxoid that was of interest to the Army and the Navy. The clearance was given after a declaration by his company that it 'never had any reason to doubt his devotion and allegiance to the United States' and a thorough investigation was made of his record both at Boston and at Pearl River."

The New Republic fulminated in 1943 against the notion that natives of India like SubbaRow and other world-renowned scientists then playing valuable roles in USA in helping to win the War were unfit for American citizenship that was 'freely granted to the most backward and ignorant Balkan peasant'. That year a number of bills were introduced in the Senate and the House of Representatives for lifting the citizenship bar on Indians. One of them reached the statute book in July 1946.

SubbaRow wished to shed the stigma of being an 'alien' amidst people with whom he had lived 25 years and had thrown his lot, but it took a year for him to get the ruling of the Immigration and Naturalization Service that he had been admitted legally into the United States. He spread the good news among his associates but he did not in the next twelve months he lived file his 'Declaration of Intention' the necessary first step to get the American citizenship.

SubbaRow felt within he was an Indian and he died an Indian.

When he died on August 8, 1948, obituaries appeared in Science, New York Times, New York Herald-Tribune and newspapers and journals in many parts of the world. The Herald-Tribune called him 'one of the most eminent medical minds of the Century'.

Yellapragada SubbaRow was not born great; his mother had to sell the little jewellery she possessed to provide for his education. Nor was greatness thrust upon him. He achieved greatness by imagination, self-confidence, love of fellow humans, and an inner compulsion to alleviate human suffering. And he did what no other Indian had ever done till then on foreign soil: he made

some of the most important and seminal contributions that were destined to transform a whole range of basic and applied sciences and save innumerable human lives. If there were a Nobel Prize for those who died virtually unknown but whose accomplishments lit the path of many who came later, SubbaRow would surely be among the first to receive it.

Even today in our country very few people know of him. The efforts of the Centenary Committee succeeded in getting the government issue a stamp in his honour in 1995. But he has not been given the appropriate recognition by the nation till today. We have given the Bharat Ratna posthumously to others. Why not to Yellapragada SubbaRow?

(Adapted from a talk at the SubbaRow Centenary Exhibition in Hyderabad's American Studies Research Centre – now Indo-American Centre for International Studies – with italicised updates). Formerly Director of CCMB, the Centre for Cellular and Molecular Biology, Dr Bhargava heads ANVESHNA the science consultancy in Hyderabad.