Course Name: I think Biology

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Institute Name: Azim Premji University

Week:1

Lecture:6

W1L6_A Tale of Forgotten Scientists - Part II

Hello everyone and welcome back to the NPTEL course, I Think Biology. My name is Prachi Gupta and In today's session, we will learn about another lesser known scientist who made significant scientific contributions. In the previous session, you learned about Janaki Ammal and her contributions in the scientific community. In today's lecture, I will talk about another brilliant Indian scientist who remained anonymous, but his contributions are a gift to humanity. To begin with, I would like to give you an overview of his discoveries he made during his lifetime. So just have a look at this slide and look at the discoveries that this person made.

He discovered methods for phosphate analysis, he discovered ATP and he went on to discover many medicines for many diseases such as anemia, tropical sprue, drugs against cancer and many antibiotics. He is even known as father of miracle medicine. I would like to give you a moment to think about who the scientist is. Look at this slide and think, can you recognize the scientist behind these wonder drugs which are still being used by the humanity? If you are not able to recognize him, let me introduce you to this brilliant mind.

His name is Dr. Yellapragada SubbaRow. In 1950, a news reporter Doron Antrim, he wrote about Dr. Yellapragada SubbaRow. He wrote that you may have never heard of Dr. Yellapragada SubbaRow, yet because he lived, you may live longer. SubbaRow made lasting contributions to many fields of biology such as biochemistry, pharmacology, microbiology, and oncology. Here is a picture of Dr. Yellapragada Subbarao. So let's learn about this researcher and his journey from a very difficult childhood to his scientific contributions.

So let's begin from the very beginning from where he was born. So he was born on January 12th, 1895 in West Godavari district of Andhra Pradesh. He was the fourth child

of Jagannatham and Venkamma among seven children. So his early life was not particularly promising. Jagannatham, his father, he had to take an early retirement from state government because of his illness and his mother, she was disciplinarian and she was determined to see her children to make good in life.

The family income since his father was retired and he was not well, so the family income was very low. They were hardly making their ends meet. So he had seen poverty and to he had this ambition to overcome this poverty. So what he did was at the age of 14, he ran away with the dream of becoming a millionaire. So he dreamt of becoming a millionaire and he decided the best way to do that is to run away to Varanasi and sell bananas to pilgrims.

He even succeeded in his plan to run away with his cousin. But his absence was soon noticed and he was brought back and then onwards his mother kept a close eye on him. So he became regular in school attendance. In 1913, when SubbaRow was just 18 years old, his father passed away and maybe that affected his studies in some ways because he failed matriculation examination twice. So we're talking about a brilliant mind and he failed his 10th exam twice.

After that, his mother had to sold her ornaments to send him to school in Madras and he finally passed the exam. After that, he finished his intermediate college and then he began pondering what should I do next. So like any teenager at that age who begins to question what should I do with my life, what should I do with my career, he had the same questions. He thought should I get involved in politics, should I help poor by being in medicine, should I just earn money or maybe just marry a nice girl, have no children and live a content life. Finally, he rejected all these options and he decided that he wants to join Ramakrishna mission and become a sannyasi.

But the problem was he could not join this mission without the permission of his mother and his mother would not give her permission. So finally, he decided to enroll in Madras Medical College and he did that in 1915. But even that time, he regarded this medical course as a temporary occupation while he practiced yoga. And for two years, he did not attend classes regularly. But after two years, he became regular.

He started working hard and diligently to fulfill his goal of helping people. So he decided to take his medical course seriously. So also at that time, since he was struggling with money, so his medical fee was funded by his friends and Kasturi Suryaprakash Rao, whose daughter he later married. So he married his daughter on May 10th, 1919. During this time, during his medical course, he was also influenced by Gandhiji and his fight for freedom.

And to support him in his way, he started wearing khadi. Even he started wearing surgical gowns made of khadi. So his nationalist views and his khadi attire offended the European professors. And despite his hard and diligent study, he only got a lesser LMS degree and not the full MBBS degree. After that, he met a young American scientist and learned about Harvard School of Tropical Medicine.

And he once secured admission in the school. But he was dependent on his elder brother's contact for a scholarship to finance his Harvard studies. But tragedy struck and his elder brother passed away due to tropical sprues and intestinal conditions. And after a week of this tragedy, he also lost his younger brother to the same disease. These tragedies in a way became a driving force for his future endeavors to fight against diseases.

Since he could not go to Harvard School and he did not have an MBBS degree, he started his career as a lecturer in anatomy and physiology at Madras Ayurvedic College. His ultimate goal was to help sick people, to heal sick people, and for which he believed that he needed a foreign education from a good university. And finally, after hard work, he received a scholarship and he could leave for Harvard two years later. He left behind his wife with the promise of returning in three years.

But he never returned. So this was the last time he was in India and he said goodbye to his family, his wife, and he never returned back from the US. He stayed in the US until his last breath. Subbarao finally came to Boston, but he came to Boston with very little money. And he had to pay part of his fee by doing odd jobs like washing up urinals of patients during night hours at a hospital. But during this time, he also worked on an unsuccessful project which involved culturing of, sorry, cultivation of entamoeba coli, but he learned research procedures while working on this project.

By June 1924, he was able to get his Harvard diploma in tropical medicine. After that, he entered Harvard Medical School for PhD program in biochemistry and he joined lab of Dr. Cyrus Fiske. When he joined this PhD program at that time, there was quite an interest and activity in the chemistry of phosphorous in living organisms.

So while working with Dr. Fiske under his supervision, SubbaRow developed a method for the estimation of inorganic phosphates in blood filtrates and total phosphate analysis in blood and tissue. And this method was correct to one by hundred thousandth(1/100000) of a grain. This method came to be known as Fiske-SubbaRow method and it has been since used all over the world for analysis of clinical and biological material. So this method was published in Journal of Biological Chemistry in 1925 and this is the first procedure to measure phosphorous in the body. It's the first
procedure that any biochemistry student learns.

And this paper, it also has a distinction of having largest citations in scientific literature. As you can see, it has more than 26,000 citations. So why this method was so popular and so important to give you an overview is phosphorous is one of the abundant minerals in our body. It is found in our bones, it is found in our teeth, so it helps in keeping our bone and teeth healthy. And it is also used in many important functions such as produce energy, keep a balanced pH and it forms our genetic material DNA and RNA.

It also helps to deliver oxygen from red blood cells to the body. So given the importance of phosphorous in our body and the diseases associated with it, as you can see, if phosphorous levels increases in blood plasma, it can lead to kidney failure, acidosis and goiter. And if the phosphorous is low in blood plasma, it can lead to softening of bones and rickets. So this method is also a very important tool in diagnosing metabolic diseases. And biochemists and pathologists, they still use this method to estimate the amount of phosphorous.

This also led to discovery of two new compounds in muscle tissue. One was phosphocreatine in 1926 and adenosine triphosphate ATP which we know as the energy currency of the cell in 1928. These two compounds, they are directly involved in muscular contraction. These discoveries, they show that how hasty was the Nobel committee to give 1922 award to MeyerHoff and Hill for linking the lactic acid cycle to muscle contraction. And however, discovery of ATP by SubbaRow and Fiske showed us that that was not the case.

Ironically, Fiske and SubbaRow did not get full credit for the ATP discovery. Around the same time, another researcher, Carl Lohmann, he also used Fiske SubbaRow method for phosphate analysis and he also discovered ATP. But he was the first to announce discovery of ATP. Hence, presently the credit is jointly given to Lohmann as well as Fiske and SubbaRow for independently discovering ATP. Although many books, they mention only Lohmann's name.

And both of them, they published their work at the same time in 1929. In 1930, SubbaRow was finally awarded his PhD in biochemistry. Despite his PhD, he was given the position of research fellow sorry he was given the position of teaching fellow, which is normally available to American graduate students who are working for their doctorate. He was still under the supervision of Dr. Fiske, but he continued to work on phosphorus compounds, which he's extracted from spleen, pancreas, liver and kidney.

And he isolated some seven to eight phosphorus compounds. Dr. Fiske, he took the full responsibility for publication, but he never published those discoveries. In the context that

SubbaRow made these discoveries of phosphate compounds and which was never published, another person, George Hitchings, who was SubbaRow's so Hitchings, who was SubbaRow's colleague in Fiske's laboratory, he remarked in 1965 that SubbaRow had isolated several phosphorus compounds, which were most likely nucleotides associated with RNA synthesis. And they had to be rediscovered by another scientist because his work was not published.

George is one of the person who got 1988 Nobel Prize in medicine. In 1935, SubbaRow had to face a very unusual situation. His supervisor, Dr. Fiske, he was being considered for promotion from associate professor to full professor. And for this, his work on phosphorus, phosphocreatine and ATP, it was taken into account.

But there were controversies surrounding these discoveries. Most of the people in Harvard, they believe that SubbaRow's share of credit for these discoveries, it was probably more or maybe at least equal to Fiske's. To save the day and help his supervisor get this promotion, SubbaRow declared that he did not make any contribution to the ideas, but he just provided a pair of hands to realize Fiske's ideas in the laboratory. This sacrifice did not let SubbaRow fulfill his own dream of becoming a full faculty member and have his own research team at Harvard Medical School. Later on, he was appointed as an instructor in 1936 and associate in 1938.

But even these positions were not completely independent teaching positions. He decided to leave Harvard Medical School and he joined as an associate director of research in lateral laboratories in May 1940. Currently, this pharmaceutical company is owned by Pfizer. Now this journey, it took him to the discovery of vitamins, antibiotics and many other drugs. During his time at Harvard, he was also trying to isolate compound from liver which he believed to be the cure of tropical sprue which had taken lives of his brothers.

But at Harvard, he did not get the facilities and he finally moved to this pharmaceutical company. In March 1945, he finally isolated folic acid from liver which is known as vitamin B9. Folic acid it’s actually an anti-sprue remedy. It's the cure for tropical sprue and it is effective in treating various kinds of anemia.

Also, it helps in fighting heart diseases. So when he isolated this folic acid, it was unaffordable. One gram of folic acid costed $4,250. But his aim was not just to isolate compounds or to discover medicine. His ultimate goal was to help sick people. After discovering folic acid which was unaffordable, he searched for alternative sources.

He isolated from fermentation growth of microbe. It still had a high cost. Then he finally synthesized folic acid. So synthetic folic acid was much lesser in price and when the

regular manufacturing began, the cost was reduced to $1.12 for 25 tablets of 5 grams each.

In India, you can get 10 tablets for Rs.10. So when the time came to put the name on the paper for announcing the synthesis of folic acid, SubbaRow chose to include his name in alphabetical order. And again, he remained anonymous for this discovery as well. As I told you that folic acid it helps in curing anemia. So how does it do that? This vitamin B9 helps in promoting the growth of white blood cells in the bone marrow which helps in fighting anemia. So from this observation, the idea to treat leukemia emerged.

Leukemia is blood cancer. So SubbaRow knew that folic acid helps to blood cells grow. So a compound that stopped folic acid maybe could slow down the cell growth. So based on this line of thought, SubbaRow and his colleagues, they started to work on synthesizing folic acid conjugates and antagonists to test his anti-leukemia drug. So he was looking for a compound which was anti-folic acid. So subbaRow keeping this in mind SubbaRowlaunched a program for possible cancer cures by manipulating folic acid molecule.

Finally, he discovered a folic antagonist, Aminopterin. And it brought remission of WBC in one of the patients. Dr. Farber tested this antagonist on a child suffering from leukemia and this drug brought remission of WBC in this kit. However, prolonged use of this drug is inadvisable and SubbaRow immediately directed all his efforts to produce a substitute with the same activity range but relatively non-toxic. Finally, he yielded this miracle drug called Methotrexate which is used to fight several kinds of cancer.

And this drug is even still used in chemotherapy today. Not only cancer, this Methotrexate, it is used to treat several other diseases such as immunodeficiency, rheumatoid arthritis, etc. During this time, he also discovered a cure for another disease, filariasis. This disease is common in tropical countries and it is spread by mosquitoes and black flies. And if it is not treated, this can be fatal. As you can see in this image that this disease can lead to inflammation of limbs.

So in this image, you have these really huge legs. So this disease is very common in tropical countries and during the same period when SubbaRow was supervising the historical discoveries in the treatment of anemia, tropical sprue, and cancer with folic acid and its modified version, he was also guiding research in tackling this disease. He finally discovered diethyl carbamazine in 1946 and it is still the most widely used drug to treat filariasis and it is recommended by WHO. This drug is commonly known as Hetrazan. Along with this discovery, he also started a program to find a broad range antibiotic.

For this, he engaged Benjamin in his team. He was a retired plant physiologist and they were working to find an antibiotic which has a broad range spectrum. So finally, they discovered aureomycin which was extracted from Streptomyces aureofaciens. So this was the first broad spectrum antibiotic which was effective against both gram-positive and gram-negative bacteria. Before this, we had an antibiotic you all must have heard of, penicillin. So penicillin was discovered a few years earlier and it was useful in treating diseases which was which were caused by gram-negative organisms.

And then we had another antibiotic, streptomycin which was effective only against gram-positive organisms. So aureomycin was the first antibiotic which was effective against both gram-positive and gram-negative bacteria. Soon after this discovery, tetracyclin was also identified. So even after this discovery of this wonder drug, in a conference SubbaRow sat in a back row and let Benjamin present the work and Benjamin became the face for promoting this drug.

And SubbaRow again remained anonymous for this discovery. Soon after when the world got to know about aureomycin, this wonder drug, soon after that SubbaRow lost his life due to cardiac arrest. He died on 8th of August. He died a stranger to fame. He was only 53 at that time. So I would just like to point this out that even though he did not achieve so much all alone, but he played a major role and provided leadership in research efforts that culminated in drugs that we are using even now. So he remained anonymous even with all these discoveries, maybe because he hardly gave any lectures and he hardly, He rarely presented his work in conferences. Instead, he allowed his co-workers to do that while he would sit back and listened to those discoveries.

Millions of us who are alive because of the drugs he dreamed and brewed are yet to hear of him. So in the beginning of the lecture, I showed you this quote by Doron and Antrim. I hope you understand now why he said those words that you may have never heard of Dr. Yellapragada SubbaRow.

Yet because he lived, you may live longer. This man went on to discovering so many wonder drugs, so many medicines for humankind that we still use today. And millions of us are using these drugs and we owe our lives to this person. And yet we don't know about him. I hope you learned something from this lecture and the previous lectures. You learned about these two lesser known Indian scientists who went on to make such an significant contributions to scientific community and to humankind.

We have similar interesting lectures planned for you during this whole course. And I hope you continue enjoying our course. See you next time. Thank you.