India’s contribution to folic acid in medicine

Anaemia has been described in the Charaka Samhita (3rd/2nd century BC) including its treatment with iron preparations. In the English language literature, the term ‘chlorosis’ was coined in 1615 by Jean Varandal from the word ‘Chloris’ (Greek: χλωρῖς) meaning ‘greenish-yellow’, ‘pale green’, ‘pale’, ‘pallid’ or ‘fresh’. In 1681, English physician Thomas Sydenham advocated iron as a treatment for chlorosis and in 1936 Arthur J. Patek and Clark W. Heath of Harvard Medical School, Boston, USA concluded that chlorosis was identical to hypochromic anaemia.1 It was Thomas Addison who in 1849 described what we know today as pernicious anaemia.2 The German physician Anton Biermer also described pernicious anaemia in 1868 and 1872, reporting it as a newly discovered disease. Paul Ehrlich in 1880 first used the term megaloblast to describe the abnormal cells in the bone marrow of a patient with pernicious anaemia.3 George Whipple in Rochester induced anaemia in dogs by bleeding them and found that administration of liver restored haemoglobin levels. Minot and Murphy suspecting that pernicious anaemia was due to a dietary deficiency, administered liver to patients and documented improvement; for this work they received the Nobel Prize in 1934.4 However, patients had to eat half a pound of liver every day till Edwin Cohn developed an extremely potent liver extract that could be eaten in small amounts or injected.5 This was followed by the suggestion from William Castle that there is requirement for an ‘intrinsic factor’ that allowed absorption into the body of an unknown ‘extrinsic factor’ in liver extracts.6 In 1948, Karl Folkers in America and a team in England, both announced that they had isolated the liver factor, a ruby-red crystalline substance named vitamin B12. At a symposium of the International Union of Pure and Applied Chemistry (IUPAC) in Delhi, Robert B. Woodward announced the synthesis of vitamin B12 (work in collaboration with Albert Eschenmoser).7,8

The paper, published in 1931, by Lucy Wills in the British Medical Journal is a landmark because the description of ‘tropical macrocytic anaemia’ suggested for the first time that there could be a cause for anaemia with macrocytes and megaloblasts in the peripheral blood other than the pernicious anaemia suggested by Addison. In the paper, she suggests ‘that these anaemia’s have the blood picture of Addison’s or true pernicious anaemia, but differ from this condition in that the typical blood picture is not associated with the other symptom-complexes’.9 She also suggests that tropical macrocytic anaemia may be primary or associated with pregnancy and other causes but that both are the same entity. These observations have great importance because for the first time the medical community considered a cause other than Addison’s pernicious anaemia for macrocytic anaemia. She makes a very sad commentary on the status of women in India in the 1930s: ‘Indian women of the hospital class are uneducated, very frightened, and suspicious. Few remain long enough for a cure, and many leave in a pitiful condition. The demands of their homes are very pressing, and neither they nor their relatives realize the importance of treatment; if a woman can crawl she must attend to her home duties.’ She goes on in the paper to describe in great detail eight cases with clinical and laboratory features and their response to treatment.

She used liver as the treatment since this was the only treatment for a macrocytic anaemia available at that time. However, ‘it must be noted that it is essential to give large doses of liver extract (up to as much as the equivalent of 600 grams of fresh liver daily) if a rapid response is to be obtained’. If she had not experimented with marmite, it might have taken medical science a lot longer to discover that macrocytic anaemia can be due to either vitamin B12 or folic acid deficiency since crude liver extract does contain small amounts of folic acid.10

Wills worked closely with Sakuntala Talpade, Robert McCarrison and Manek Mehta in attempts to find a supplement that might overcome the deficiency they were observing. They tried many substances on rats. Wills was concerned, however, that an infection common in the rats might be playing a role in their anaemia, so she decided to test some dietary interventions in monkeys. One particular monkey did especially poorly, and for reasons which are not recorded—perhaps in desperation—she tried the cheap yeast extract, marmite. It had a dramatic effect. Thus, after all the intensive examination of diets and exhaustive testing on rats, it was a chance intervention with a single animal that led to the breakthrough. Wills had taken the first step to the discovery of folic acid.11

In this paper, she describes her use of marmite in patients with tropical macrocytic anaemia and notes that it was effective and the response to this agent was similar to and, in some cases, more striking than the response obtained with liver extract. In the conclusion to the paper, she makes this remarkable statement: ‘The question must, however, remain unsettled until further work can decide the common factor in the two extracts which is active. At present it is only possible to state that in marmite, and probably in other yeast extracts, there appears to be a curative agent for this dread disease which equals liver extract in potency, and has the advantage in India of being comparatively cheap and of vegetable origin.’ Folic acid had not been discovered at that time and the term ‘Wills factor’ or ‘Vitamin M’ was coined to describe the agent in both liver and yeast extracts which produced a response in tropical macrocytic anaemia.

The synthesis of folic acid was accomplished in August 1945 by Robert Angier and his coworkers under the supervision of Yellapragada Subbarow at Lederle laboratories. The Indian contribution to folic acid through the work of Wills and Subbarow is path-breaking.12

The reader would do well to read about the life and work of Lucy Wills in the James Lind Library Bulletin: Commentaries on the history of treatment evaluation by Hilda Bastian entitled ‘Lucy Wills (1888–1964), the life and research of an adventurous independent woman’.13 Hoffbrand refers to her ‘as aristocratic, independent and radical in outlook, critical of established conservative medical and scientific committees. She rode to work on a bicycle rather than in a large car as did many of her colleagues’.14 On
returning to England, she did what is probably the first randomized trial to determine the effect of iron supplements in pregnancy and in her own words: ‘The laboratory workers were not told which patients were receiving iron, but after a few visits it did not require a Sherlock Holmes to ascertain the nature of the capsules being taken.’

REFERENCES
4. Minot GR, Murphy WP. Treatment of pernicious anemia by special diet. JAMA 1926;87:470–6.

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Obituaries

Many doctors in India practise medicine in difficult areas under trying circumstances and resist the attraction of better prospects in western countries and in the Middle East. They die without their contributions to our country being acknowledged.

The National Medical Journal of India wishes to recognize the efforts of these doctors. We invite short accounts of the life and work of a recently deceased colleague by a friend, student or relative. The account in about 500 to 1000 words should describe his or her education and training and highlight the achievements as well as disappointments. A photograph should accompany the obituary.

—Editor