

Rustom Jal Vakil (1911-1974) – Father of Modern Cardiology

A Profile

SPK Gupta



THE MID-CENTURY medical world was excited. The lay press quoting accounts at medical meetings and reports in medical journals carried exciting stories. The *U.S. News and World Report* said, 'Mentally retarded children improved in behaviour, developed higher IQs. Patients with the excruciating heart pains of angina pectoris had both severity and frequency of attacks reduced. Dogs were cured of carsickness; mares that spurned foals were made normal. Skin diseases have been made less severe, and intolerable itching relieved. Prospects for recovery in mental disease have risen to 90 per cent from 65.'

The Reader's Digest narrated the story of an 18-year-old Indian student whose mind was disturbed by failure to pass an examination and, restless and excited, talked continuously but without sense, became resentful, even violent, refusing food and resisting all efforts of his parents and friends to calm him. Forcefully administered a drug derived from an ancient root extract that Indian vaidyas had used for centuries, the boy was quieter within a few days, eating again and sleeping and was completely normal within a fortnight.

LIFE International said the extensive use in psychiatry of the drug that calmed mental patients, reduced anxiety and made them more amenable to further treatment heralded a war on mental disease. It said the expected breakthrough was the fruit of an international detective hunt that began with the report of Rustom Jal Vakil of Bombay's KEM Hospital that the herb snake-root had given marked relief to 50 victims of high blood pressure. Vakil's report had excited the interest of Dr Robert Wilkins of Boston's Massachusetts Memorial Hospital. Wilkins found it was not only very effective with high blood pressure but made his patients relaxed, at ease and free from worries. Dr Nathan S Kline of New York's Rockland State Hospital thereupon tried the drug on 411 desructive, assaultive and suicidal mental patients: incidents of violence were reduced by a third. Longer tests at a Modesto (California) hospital produced improvement in 59 of 74 patients given the drug, and eight of them became well enough to be released.

Meanwhile French researchers synthesised a drug they called chlorpromazine which too eased anxiety by blocking, like the snake-root, the transfer of impulses between the hypothalamus, seat of emotions, and the cerebral cortex. Dr Henri Laborit, a Paris obstetrician, found it relieving nausea as well as anxiety among pregnant women; all but three of 38 mental cases treated by two Parisian psychiatrists showed substantial improvement.

Psychiatrists soon noted that reserpine and chlorpromazine were more potent together than when taken alone. Patients of Dr H B Elber of New York Medical College was one who combined them and obtained substantial relief in 60 to 85% of his high blood pressure patients *TIME* reported.

Dr. Vakil was honoured in 1957 with the prestigious Albert Lasker Award, the American Public Health Association citing him for his 'brilliant and systematic studies on rauwolfia in hypertension and his effective bridging of the gap between Indian experience and that of Western medicine'.

A 'historical' 1949 paper in *British Heart Journal* by Dr Vakil had summed up ten years of his careful conscientious personal work, added the opinions of some 50 other physicians who had worked with rauwolfia in hypertension and produced a document

which brought the drug finally and decisively into Western medicine. Reserpine, the rauwolfia alkaloid, was a powerful tranquilizing agent, a valuable addition to psychiatric therapy and, together with chlorpromazine, opened the way, as the Lasker Award citation noted, for 'an entirely new method of study of mental disorder itself'.

BORN in Bombay on 17th July 1911, Rustom was still in school when he lost his father Dr Jal Vakil, a busy general practitioner, but his mother Jerbanoo ensured he had a very good education at the Elphinstone College and Royal Institute of Medicine and accompanied him to London when he secured admission at the St Thomas Hospital Medical School.

Returning in 1938 to India with an MRCP and an MD of London University, Rustom Vakil built up a large private practice, served as physician and teacher in Bombay hospitals and medical colleges, and then restricting himself to the treatment of heart ailments became the most sought-after cardiologist in India. He was perhaps one of the first to introduce cardiology as a speciality in the country.

Early as heart specialist Dr Rustom Vakil came up against the persistently high mortality from hypertension in spite of the large number of recommended measures of treatment and was forced to admit if only to himself 'the futility or helplessness of the situation'. Most of the expensive and fashionable preparations extensively displayed on the market were all useless and at any rate less effective than simple sedative measures. With new drugs and measures introduced amidst much hype both in the medical profession and laity not living up to claims made on the basis of a few stray experiences and clinical impressions, Dr Vakil learnt to look for carefully controlled clinical observations and firm establishment of therapeutic value of any new remedy.

But even he could not ignore the unprecedented popularity and growing demand in India over a ten-year span for the dried root of *Rauwolfia Serpentina* after it was introduced to the market in tablet form. There was hardly a patient with high blood pressure who had not tried it. One manufacturing firm alone claimed to have sold over 50 million tablets.

Variously known as sarpagandha, patala gandhi, dhanmarna and covanamilpori, the root of the Serpentina plant - a large climbing shrub found in the Himalayas, the Deccan Peninsula, Java and Malaysia - had been used from ancient times as an antidote to the stings and bites of insects and poisonous reptiles, as a febrifuge, a stimulant for uterine contractions, for insomnia and most of all for insanity.

The snake-root plant legend has its origins in the story of a mongoose which would first chew upon its leaves to gain strength before engaging a cobra in combat. Its legendary powers soon gained weight when a demented victim ate slices of the root and was relieved of madness and a vaid found a freshly ground paste of its leaves was a good antidote for poison. The smooth leaves and snake-like roots of the small shrub with pink or white blossoms found itself centuries ago in the pharmacopoeia of ayurveda as sarpagandha. Vaid prescribed its leaf juice and powdered root for ailments ranging astonishingly from epilepsy, insomnia and insanity to dysentery, diarrhoea and cholera to headaches and blindness; it was a standard for treating fevers, it was applied as an antidote for insect and snake bites; and was customarily used in Bihar as a sleeping potion for infants.

The plant itself was known in the West ever since it was named by a 17th century botanist as *Rauwolfia Serpentina* in honour of Dr Leonard Rauwolf, the German botanist of the prior century whose extensive plant collection remains till today on the University of Leyden herbarium sheets. Most European and American physicians however dismissed its usage as implausible Indian quackery. It was given to Drs Salimuzzaman Siddiqui and Rafat Hussain Siddiqui of Delhi's Ayurvedic and Unani Tibbia College to make the first modern scientific study of the snake-root plant. The Siddiquis obtained the roots from a Patna bazaar, analysed them in the Research Institute of the College, and reported in a 1931 issue of the *Journal of the Indian Chemical Society* of their isolation of five crystalline alkaloids. Of the alkaloids, three were white crystals and named ajmaline, ajmalinine and ajmalicine after Hakim Ajmal Khan the founder of the Research Institute and the remaining two were bright yellow crystalline substances and were labelled serpentine and serpentinine. Tested by them in experimental frogs, none of the five yielded any promising results.

At about the same time the *Indian Medical Record* carried a report by two physicians, Dr Gananath Sen and Kartick Chandra Bose, of their independent isolation of two alkaloids - probably the same as two of the five isolated by the Siddiquis - their success with them in inducing a mild lowering of blood pressure in experimental animals and their clinical trials subsequently.

While they could not substantiate the broad claims made by those who extolled *Rauwolfia* as an 'infallible specific' in the treatment of insanity, Sen and Bose had found that insanity with violent symptoms readily yielded to it. 'Doses of 20 to 30 grains of the powder twice daily produce not only a hypnotic effect but also a reduction of blood pressure and violent symptoms,' they reported. 'Within a week usually the patient's senses are restored, though he may show some mental aberrations. Usually the treatment has to be continued for 4 to 6 weeks (sometimes

more) the doses being reduced gradually.' It was contra-indicated in the demented and morose types of insanity usually characterised by low BP and asthenia. Likewise it was not completely effective in the treatment of hypertension. It promised to be a valuable addition to the armamentarium of the physician, they said and commended pharmacological and clinical studies. But medical men outside India declined to believe the two physicians of India.

In India however an ever-increasing number of patients with high blood pressure and manic forms of insanity began to be treated with tablets made from powdered *Rauwolfia* root or liquid extracts of the material. And the snake-root plant received increasing attention of chemists and pharmacologists including Raymond-Hamet in Paris, van Itallie and Steenhauer in Leyden, Joseph Koepfli in Baltimore and, especially, Ram Nath Chopra at the School of Tropical Medicine in Calcutta. Researchers under Chopra's direction conducted an official survey of Indian remedies and reported in a succession of papers published beginning 1933 in Indian chemical and medical journals that crude *Rauwolfia* root possessed remarkable ability to produce sedation and lower BP, and alkaloids like ajmaline isolated by the Siddiquis had an indubitable pharmacological action. But bafflingly enough none of the alkaloids isolated until then could match alone or together the tremendous activity of the whole root, and Chopra talked about 'unknown principles' yet to be found in the root. By 1944, they traced the activity to a resin fraction of the root but their amorphous material defied further analysis. They lacked the required analytical methods, devices and tools.

Meanwhile clinical use of *Rauwolfia* increased steadily and a million patients were estimated to be receiving it for relief of high blood pressure alone in the early years of World War II. Dr B B Bhatia of Lucknow's King Edward Memorial Medical College wrote in a 1942 issue of *JMA*: 'I have no hesitation in saying that in *Rauwolfia Serpentina* we have a drug which is far superior in its effect on high blood pressure to those which we have so far used . . . The drug is particularly useful in relieving the nervous symptoms of high blood pressure such as headache, tinnitus, vertigo, giddiness, insomnia . . . Every patient remarked that he got very good sleep with this drug . . . the drug is not curative but is undoubtedly the best for the relief of symptoms caused by high blood pressure.'

Intrigued, Dr Vakil conducted a trial and found it useful 'in a percentage of cases of hypertension' but cautiously observed that indications and suitability of the drug remained to be worked out. And who was better to do the job of determining if the enthusiastic reception was

warranted than Rustom Vakil himself? He took up the investigation.

He selected fifty willingly cooperative regulars among the hundreds who came to his clinic with essential hypertension. On the diagnosis being confirmed with routine clinical examination, the 30 males and 20 females aged 39 to 76 years (average 59) were checked for BP and put on a daily sedative capsule for two weeks and then the 'pre-treatment' BP was taken.

They were then given one tablet of 'serpina' (made from dried root of *Rauwolfia Serpentina*) thrice daily after meals for four weeks, the BP being recorded weekly, their medication stopped for four weeks and BP recorded fortnightly and then a second course of 'serpina' tablets administered for two weeks and BP recorded at the end for the last time. The analysis of the nine sets of BP readings was then made.

Within a week of the serpina therapy, over 70 per cent of the hypertensives showed an average drop of 13 mm (ranging from 2 to 38 mm) in systolic blood pressure, and an average drop of 6 mm (2 to 18 mm) in diastolic pressure.

After four weeks of therapy, over 80 per cent of patients displayed a 21-mm drop of systolic BP and a 11-mm fall in diastolic pressure, on an average. The hypotensive action was apparent in 91 per cent of cases two weeks after stoppage of treatment and in 74 per cent even after four weeks of no treatment.

The response to the second course was almost as good as the first.

R. Serpentina appeared to be a perfectly safe remedy as it was devoid of any serious or toxic ill effects.

Vakil had the satisfaction of seeing encouraging results from the serpina therapy. In most cases it was capable of lowering both systolic and diastolic BP. Although its action was temporary in many cases, it could be reproduced successfully by a second course.

Serpina satisfied all criteria for a successful hypotensive agent formulated by W Evans and O Loughnan in the first volume of the *British Heart Journal* in 1939. And Vakil pronounced cautiously that 'it has a definite place in the treatment of cases of high blood pressure'.

The 1949 Vakil paper in *BHJ* summing up 10 years of his own conscientious work and the opinion of 50 other physicians brought the first proven remedy for high blood pressure into Western medicine. Millions suffering from hypertension were treated with serpina following this *BHJ* paper.

Vakil is also credited with opening a new epoch in the therapy of mental disorder. For with the isolation of

reserpine alkaloid from the snake-root following the publication of his historic paper and the observation it produced severe depression as a side effect, psychiatry began, as already noted, to use it as a tranquilizer to control agitated psychotic patients. While phenothiazine tranquilisers have largely replaced it in psychiatry, reserpine continues to be an experimental tool in the study of psychosis.

Vakil essentially removed 'a block in medical communication'. As the American Public Health Association said in the 1957 Albert Lasker Award souvenir, Vakil focussed attention on an important drug used in Ayurveda for hundreds of years and had been the subject of modern scientific research in India since 1931 and repeatedly reported in journals as a psychiatric and anti-hypertensive therapy. Whereas others had overlooked them and followed innumerable fruitless leads, Vakil by his trail-blazing and epoch-making paper got hailed as the Father of Indian Cardiology and Father of Rauwolfia. In retrospect we can say Vakil was indeed the Father of Modern Cardiology in that he should be given much of the credit for the introduction of an ancient folk remedy of the East into Western medicine and 'inspired new and successful line of treating both heart and mental or emotional ailments'. ('Autobiography of Science' by Moulton and Schiffers, 1960).

UNLIKE Calcutta's Chopra associates, Dr Emil Schlittler, a Swiss chemist, had all the required analytical methods, devices and tools at his bench in the CIBA Laboratories at Basle. He obtained a quantity of the crude from company representatives in India, put it through a simple extraction process, and had the sample tested in animals at the pharmacology lab. 'Moderately effective as sedative,' the pharmacologists said. 'Moderately effective in reducing blood pressure.' Schlittler concentrated the crude a little further and isolated a couple of grams of crystalline ajmaline of the Siddiquis and put it on a lab shelf.

Sir Robert Robinson of Oxford University, visiting CIBA Laboratories in September 1947 and told by Schlittler of his investigations, asked for 40 grams of ajmaline to investigate its chemical structure. Enthused by the request, CIBA chemists by early 1948 prepared and shipped to Oxford nearly a hundred grams of ajmaline.

Schlittler was loth to throw away the mother liquors – which had all the *Rauwolfia* chemicals minus ajmaline – and put his students at the University of Basle on getting out 'the other alkaloids'.

After the sensational 1949 Vakil paper, they got out serpentine, another of the Siddiquis' alkaloids, worked out its chemical structure, and began to look at an additional fraction – the muddy brown residue. A purified sample brought from pharmacology the electrifying query: "What is this material? It has unusual activity". It

was indeed the resin fraction that had baffled Chopra's chemists in Calcutta. Schlittler with Dr Johannes Muller used paper chromatography and counter-current extraction methods to concentrate the resin and split it into its fractions. One fraction, seen through the microscope as a tiny clump of shining white crystals, was turned over to pharmacologist H J Bein for animal tests. Schlittler, Muller and Bein reported in September 1952 their isolation of the sedative fraction of Rauwolfia in 'pure crystalline form'. Their reserpine in remarkably low doses kept rabbits and dogs quiescent for several hours. The animals could be easily aroused – the sedation was unlike what was induced by barbiturates. A few months later, Bein reported that reserpine also reduces blood pressure.

The single chemical complex responsible for the sedative and anti-hypertensive activity of Rauwolfia was suitable for injection and ready for trial as substitute for the unstandardised tablets of crude serpina.

CIBA sent botanists and buyers to India to collect snake-root by cartload and air express it to Basle to get enough reserpine for chemical and pharmacological studies, and for clinical trials. Reserpine was found to produce sedation and relaxation by acting on the deep-seated brain centres, and to lower blood pressure by involving the regulating centres in the hypothalamus. Clinical trials began all over the world – in Switzerland, Germany, USA and India.

Dr Robert Wilkins of Boston, first Western physician to confirm Vakil's findings with serpina, was also the first to report formally on reserpine. He told a medical meet at Memphis, Tennessee: '... we can say that Serpasil (brand name for reserpine) appears to produce all the actions of crude Rauwolfia.' Rauwolfia therapy thus arrived in America in 1954.

But, its toxic side effects including nightmare, parkinsonism and gastro-intestinal disturbances and availability of other hypotensive drugs have limited reserpine in medical practice. Vakil's place in the history of medicine as an innovator nevertheless remains undimmed. Reserpine was subsequently found to deplete the brain of norepinephrine and serotonin and also to deplete the peripheral sympathetic nerve terminals of norepinephrine. This and other adrenergic inhibitors barring alpha-1 receptor blockers are not recommended for routine initial therapy because 'they may cause subtle fluid retention, leading to pseudotolerance, and they also have higher adverse effect profiles than the drugs recommended for step 1,' says The Merck Manual. 'However, alpha-2-agonists and reserpine are excellent step-2 drugs.'

The wide range of options the cardiologist now has is attributable, historically, to the variations in potency of different batches of serpina tablets which prevented even experienced clinicians from prescribing accurate dosages

for individual patients. That gave the push for an international effort to synthesise and employ therapeutically many other drugs including reserpine for treatment of the malady.

AFTER a study of 360 cases of coronary heart disease, Vakil described the 'pre-infarction syndrome' in the May 1964 issue of the *American Journal of Cardiology*. Other clinical entities medicine owes Vakil are 'hexalogy of the heart', 'giant cell arteritis in aortic regurgitation', 'transitory pulsation in coronary thrombosis' 'gummatous forms of rat-bite fever' and 'subacute pulmonary oedema'. He introduced a new classification for abnormal heart rhythms. He also made practical suggestion for starting a drive against the increasing incidence of coronary or atheromatous heart disease.

Vakil got interested in *Nardostachya jatamanshi*, another herb described in ayurvedic literature, and wrote about its utility in the treatment of neuropsychiatric disorders. He was a gifted speaker who combined a fluency of speech and a sense of humour in his public lectures on medicine. He was acclaimed for his *Illustrated Weekly of India* series on 'The Medical Legacy' of ancient India.

He was showered with many national and international honours including Padma Bhushan, Dr B C Roy Award, Shanti Swarup Bhatnagar Award, Dhanwantri Award, and fellowships of the Royal College of Physicians of London, the American College of Cardiology.

Vakil was a member of the American Heart Association and a Director of All India Heart Foundation, New Delhi.

He delivered invited orations and lectures all over India. Among these were the Sir Nilratan Sircar Lecture (1957), the Arustha Memorial Lecture (1965), the Foundation Lecture of the *Maharashtra Medical Journal* (1965), the Vythilingam Oration (1967) and the Awalananda Das Memorial Lecture (1970).

Besides his long association with the K E M Hospital, he was visiting cardiologist at the Nanavaty Hospital and the Bombay Hospital among others.

His 'Clinical Diagnosis' was a popular textbook, and 'Diagnosis and Management of Medical Emergencies' was highly commended. He edited the API's 'Textbook of Medicine', and endowed API's 'Mrs J N Vakil Medal and Lectureship'.

A long-cherished wish came true on 28 September 1974 with the establishment of the Vakil Institute of Cardiology and Research Centre at the K E M Hospital devoted to the prevention, early detection and treatment of diseases of the heart to which he personally contributed one lakh rupees. Another four lakh rupees were donated by friends and admirers.

Less than two months later, the world was stunned by Vakil's untimely death on November 20 from aortic dissection and myocardial infarction – the very ailments he had treated in a medical practice spanning four decades, personally extending the lives and improving quality of life of thousands, and influencing similar enrichment of thousands of others through the medications he introduced and the medications that he inspired others to introduce.

Sources

1. Rustom Jal Vakil by Aspi F. Golwala in *Biographical Memoirs of the Indian National Science Academy*.
2. *A Clinical Trial of Rauwolfia Serpentina in Essential Hypertension* by Rustom Jal Vakil. *British Heart Journal* 1949; 2: 350-5.
3. The Rauwolfia Story (1945: Ciba).
4. New Drugs (US News and World Report, November 11, 1955).
5. Pills for the Mind (TIME, March 7, 1955).
6. After Polio, War on Mental Disease? (LIFE *International*, June 27, 1955).
7. Reserpine (The Reader's Digest, December 1955).
8. Indian Doctor Named Recipient of Lasker Award (Wireless Bulletin, USIS, Madras, November 8, 1957).
9. Sarpagandha: The Wonder Drug of India by K Vedantam (THE HINDU, December 18, 1960).
10. A communication dated 16 March 1956 to the author from Bengal Chemical & Pharmaceutical Works.
11. Arterial Hypertension (Section 16, Chapter 199, THE MERCK MANUAL).

The Author is Biographer, Science/Medicine Historian and Editor (1988-91) of Press Trust of India.

Address

ELLA'S COTTAGE
B-108, Gulmohar Park, New Delhi-110 049, (INDIA)
Phone : 656 9703.