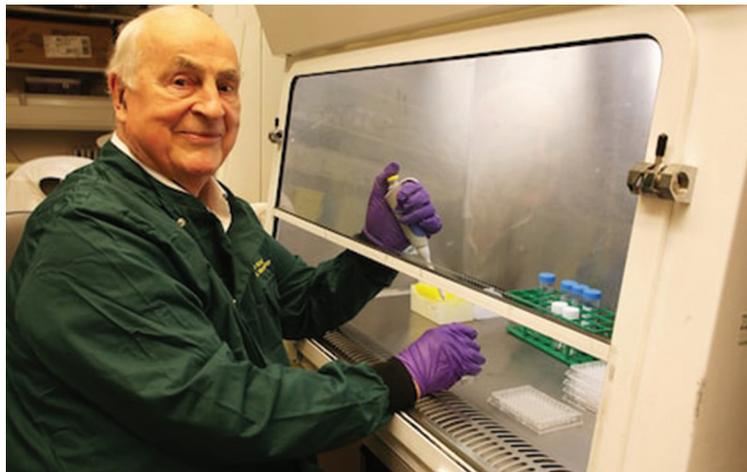




Obituary



Prof. Denis A. Mitchison (1919-2018)

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Lives of great men all remind us
We can make our lives sublime
And in passing leave behind us
Footprints on the sands of time

Henry Wadsworth Longfellow

Denis A. Mitchison, a key Founding member of the internationally-known Tuberculosis Research Centre [TRC, now ICMR-National Institute for Research in Tuberculosis (NIRT)] in Madras (Chennai), India, passed away in London, U.K. on July 2 this year at the age of 98. His achievements and traits can be characterized in two quotes.

*Talent hits a target no one else can hit. Genius
hits a target no one else can see*

Arthur Schopenhauer

*God gives talent. Work transforms talent into
Genius*

Anna Pavlova

Mitchison was a close friend and a shoulder-to-shoulder research collaborator of the legendary

Dr Wallace Fox (TRC Founder Director) who made waves with the 'Madras Classic' of late 1950s, a randomized controlled trial of Home treatment and Sanatorium treatment in patients with sputum-positive tuberculosis. With the backdrop of his stellar background experience of pulmonary tuberculosis, through the first randomized trial of streptomycin versus bed rest in the U.K. in the 1950s, Mitchison first came to Chennai in 1956. He then jump-started to establish a comprehensive diagnostic and research laboratory, to fit into his thought processes that the progress of clinical evaluation of any chemotherapy in pulmonary tuberculosis in humans could be modelled well through carefully designed and randomized *in vitro* and *in vivo* laboratory tests that could be quantitatively evaluated and correlated. His small but highly talented young team of colleagues in Chennai successfully established a laboratory and experimental animal house of his specifications, for providing bacteriological, pathological, biochemical, pharmacological and animal experimental models to these clinical trials. A series of studies then demonstrated that patients could be successfully treated in their homes, a finding that led the revamping of the National Tuberculosis Treatment Programme of India and that of

other developing countries, and had major implications on the WHO's global treatment policies.

Mitchison was a brilliant analytical bacteriologist and pathologist who piloted a number of studies which established that Indian strains of *Mycobacterium tuberculosis* were a class different from European and African strains in terms of drug sensitivity, hydrogen peroxide sensitivity and virulence in the guinea-pig. However, these differences did not significantly affect the outcome of chemotherapy. In a subsequent clinical trial of monotherapy with isoniazid [in comparison with treatment with isoniazid plus para-aminosalicylic acid (PAS)], the findings of serial serum isoniazid concentration studies (in terms of peak concentrations and coverage attained with isoniazid) opened the gateway for the concept of fully supervised intermittent chemotherapy. Mitchison's role in the design of NIRT's controlled clinical trials, their conduct, data analysis and interpretation continued long after he left the shores of Chennai, and the postal authorities of the U.K. must have made a tidy fortune with his barrage of letters to his deputies in the NIRT that came with a serial number so that they would be read in the right sequence!

Other significant achievements of Mitchison in Chennai were as follows: (i) evolving and validating, through a series of statistically well-designed experimental studies, an index to measure the virulence in the guinea pig of strains of tubercle bacilli, and thereafter demonstrating the existence of consistent differences between patients, (ii) reporting the absence of an association between the virulence of Indian strains and several pre-treatment characteristics, and the presence of a significant association with response to isoniazid therapy, (iii) identifying important differences between Indian and British strains in other characteristics also, such as susceptibility to hydrogen peroxide and sensitivity to PAS and thioacetazone, and (iv) building a strong indigenous human-resource element by providing opportunities for training the local staff, through International Fellowships, in his London laboratory.

These achievements were largely due to the diligence, patience and perseverance of Mitchison, and are noteworthy as neither trained staff nor automated techniques were available at the time. After this outstanding stint of one year in Chennai, Mitchison went back to his parent institute in London, the Royal Post-Graduate Medical School at Hammersmith

Hospital, as Director of the MRC Unit on Drug Resistance in Tuberculosis. His close involvement with NIRT persisted however, for the next three decades through the WHO short-term consultant visits, long phone calls and epic-length letters specifying minute details to successive batches of staff and colleagues at the NIRT.

It would be no exaggeration to say that the brain waves on principles of chemotherapy that were evolved and tested in Chennai and several BMRC (British Medical Research Council) sites such as East Africa and Hong Kong had their origin in Mitchison's head. His knowledge of the design of experiments, bias prevention techniques such as randomization and 'blinding', and statistical techniques was self-taught but profound, and the 'Split-plot' design, analysis of variance and component analysis were his favourites. It is true, although it may seem unbelievable, that he often had qualified statisticians like me in a spin---not surprising though if one recalls that he was a nephew of the famous biometrician-biologist, J.B.S. Haldane.

On his return to London, Mitchison, with his deep underlying understanding of drug-resistant and drug recalcitrant bacteria, concentrated efforts on their treatment with multidrug therapy and the evolution of pragmatic 6-month short-course regimens including rifampicin and pyrazinamide. He continued these studies even after moving to St. George's Hospital in 1985 after retirement from his tenure at Hammersmith Hospital. He developed a technique for measuring the early bactericidal activity of drugs to rank their prognostic importance, and this subsequently became an essential first step in all studies of the clinical development of new drugs. He introduced the idea of an 8-week phase II study, having the proportion with negative cultures as the standard outcome measure. He elaborated on several new anti-TB drugs and involved himself in high-dosage Rifampicin trials. He plodded on gamely until he turned 95, and only then stopped regular work.

There are some unique characteristics of Mitchison that are etched firmly in the hearts of his colleagues. He was a perfectionist and often used to undertake jobs that some might have considered menial, such as repairing a packaged gas plant at midnight to ensure it would be functional the next morning to keep the lab going at 0700 h. He used to standardize the 3-mm loop size of the platinum wire to lift exact amount of tubercle

bacilli from L-J (Lowenstein-Jensen) slopes for drug sensitivity tests. Another was his probing mind that came up with an outstanding hypothesis to explain the results. He speculated on reasons for lowered virulence of Indian strains of tubercle bacilli and propounded such imaginative theories that Gardner Middlebrook, a professional rival, wrote him a warm congratulatory letter! He was an outstanding personality and leader that NIRT was privileged to have from its very inception.

Prof. Mitchison, as he preferred to be addressed, authored 250 papers in reputed scientific journals, was a member of innumerable Scientific Committees, and received several honours, including the Medal of Honour from the Union in 1987, British Thoracic Society Medal in 2000, the Stop TB Partnership

Kochan prize in 2008, and at the age of 96, the Union Medal in 2015 for 'an outstanding contribution to the control of tuberculosis' by his scientific work and actions in the field.

On the personal plane, Mitchison was a warm and kind-hearted person with a touch of regality, a good teacher, a fair judge of persons and situations, a reliable friend and excellent host, and all that goes with a distinguished personality whose memories will live forever.

S. Radhakrishna

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