The other Bose: an account of missed opportunities in the history of neurobiology in India

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Despite their antiquity, Indian medical traditions are often viewed as 'traditional' and pre-scientific, and not having contributed much to the recent developments in medicine. A series of systematic observations regarding the uses of reserpine, initially derived from traditional medicine, was critical to the entire field of modern psycho-pharmacology, as well as providing useful insights into neuro-biology. However, despite the early promise of the work on reserpine in India, most of the later research work, and industrial development, was accomplished outside India. A locally available, inexpensive, plant-based product, laid the base for a multi-billion industry of anti-depressants and anti-psychotics, based upon the insights provided by reserpine. We need to pay more attention to the local sciences, as well as our botanical and human diversity, to develop novel strategies to understand neurobiology, and thus combat neuro-psychiatric diseases, and many other complex disorders.

The encounter of formal western medicine and South Asian medical traditions can be approximately dated to the advent of the Portuguese. For sometime before this, Arab medicine had been the bridge of knowledge and tradition between Asia and Europe, and successfully integrated and extended the two schools of knowledge, including medicine. The direct access of the Europeans to Asia after the sea routes were opened, created a new dynamics.

One of the earliest European practitioners in India was Garcia D 'Orta, the celebrated Portuguese physician, who was emphatic in his praise of Indian medicine men, and their knowledge of botany. Later travellers in Goa noted that '*The Portugals when they are sicke, disdaine not to conferre with those Pagan Phisitians, & the Archbishop with all the Church men trust more in them than in the Portugals themselves: this is the reason why these phisitians are wonderfully honoured, and gather great wealth*'[1]. The fame of Indian medicine thus reached Europe, and by the end of the 17th century, d'Orta's books had been translated into many European languages. Ambrose Paré, the French physician, translated the book, and from there the English derived more detailed knowledge of medicine in India, including treatment of mental disorders[2]. This, and similar books, were being used by the physicians coming out to India as employees of the East India Company.

By the late 17th century, the use of Indian plants (Cassumuniar?) for the treatment of melancholy was already known, as one author notes '*A very Eminent East-India Chyrurgion assured me, he had used this Root in Melancholy Hypocondriack*'[3]. As these doctors noted, '*The Indians are very excellent Botanists, admirably skilled in the nature, and use of Plants, and having an extra-ordinary variety of them have improved Galenical Physick to a very great height*'. This reliance in Britain, on medicines based on plants from Asia, soon gave rise to critical comment, as it was felt that 'local' medical traditions in England and Europe needed to be preserved against the near monopoly of medicines from India and Arabia. Discontent over monopolistic cartels controlling access to drugs is thus not a new pre-occupation! One of the drugs identified was Sarpagandha (also known as Chandrika; the link between the moon and madness having universal acceptability; now identified as *Rauwolfia serpentina*), which had been described in the Ayurveda, along with several other drugs.

The subcontinent thus became a rich resource for medical discovery. Rumpf, a botanist with the Dutch East India Company, identified the reserpine plant as such in 1755, and the entire genus was named *Rauwolffia* by Linnaeus in honour of Leonard Rauwolf, a German botanist who travelled to the Middle East and described several medicinal plants in the previous century. Rumpf was made aware of the use of this drug for treating insanity and recorded it[4]. However, by the 19th century, this drug was essentially neglected and forgotten. The genus *Rauwolffia* is widespread, and other species such as *R. caffra* are well established in African folk medicine as treatment for insanity. It is a member of the Apocynaceae family, which also contains vinca (anti-cancer drugs), cerebra and apocynum (contain Ca channel blockers and cardio-toxins related to digitalis) and many other common plants. Why one family of plants has such an array of toxins for components of the signalling systems in animals is an intriguing area for future research.

The modern history of reserpine

Modern cosmopolitan medicine, as currently practised, was introduced to India by establishing medical colleges under colonial influence, from 1835 onwards. Contributions by Indian practitioners began accumulating soon, and there were several notable attempts to develop syncretic models that would combine indigenous and traditional knowledge systems, and 'western' medicine. However, the reluctance of the colonial administration to accommodate these traditions (especially after 1857), or even provide training, seriously affected any attempt towards such synergy. Moreover, scientific and administrative opportunities were limited for Indians in the medical profession, but the growing number of Indian doctors in positions of authority after the First World War changed the face of medical practice and research. There was much greater involvement of Indians in medical research, and in addition, there was increasing involvement in the entire edifice of 'modern science' by the 20th century. The works of J. C. Bose, C. V. Raman, S. Ramanujan, M. Saha,

Satyen Bose and many others in the early 20th century are some well-known examples. Science academies were started, and interestingly, there were several psychiatrists involved in the founding of the INSA, New Delhi.

In this context, the seminal paper by Gananath Sen and Karthick Chander Bose in 1931 is quite interesting. They reported on the use of an alkaloid extract from the *Rauwolfia serpentina* plant in the treatment of hypertension and 'insanity with violent maniacal symptoms'. They noted that dosages *'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... within a week usually the patient's senses are restored, though he may show some mental aberrations*'. These observations did not travel much outside India. It is, however, important to realize that this was approximately the period when insulin coma (1933), metrazol therapy (1937) and malaria therapy (1918) were introduced; none of which have withstood the test of time, despite Wagner–Juaregg's Nobel Prize in 1927 for malarial fever therapy. Treatments for psychiatric disorders simply did not exist, and could not even be conceptualized, as our knowledge of neurobiology was insufficient.

The paper on the effects of reserpine, however, excited much interest within India. Chopra and colleagues, in a series of papers demonstrated its use in both hypertension and insanity. However, Kartick Chander Bose, unlike Girijashanker Bose (a psycho-analyst who was in correspondence with Freud and is a subject of several books and hundreds of articles on the 'psyche' and colonialism), is hardly known in scientific or even in psychiatric circles, and his biography or subsequent scientific career is difficult to trace.

Thankfully, the descriptions of Sen and Bose interested scientists other than physicians and psychiatrists too. Siddiqui and Hussain, two chemists working at Aligarh Muslim University (AMU) were able to extract several compounds, such as ajmaline, ajmaciline and serpentine almost immediately (1931)[5]. Whether Siddiqui was more familiar with the scientific developments in Calcutta (he had a close link to Shantiniketan and was a painter after the Bengal school) that may have whetted his curiosity is not known. Siddiqui had studied at the AMU and at Shantiniketan, before doing doctoral work in Germany and the UK, and was a painter and musician in addition to being a scientist. He was an early scientist in the CSIR, New Delhi and is also credited with developing the indelible ink that is used even now during elections.

However, these two scientists could not extract reserpine. While they noted the actions of the alkaloids on the heart, they could not take this much further as catecholamines had not yet been discovered. The compounds ajmaline and ajmaciline were so named in honour of Ajmal Khan, the famous Unani physician of Delhi, who had established a college that provided training in both Unani and Ayurvedic medicine in Delhi. Ajmal Khan was strongly opposed to the growing divisions within the Indian medical traditions along religious lines, and the efforts to identify Unani medicine exclusively with Islam[6]. He was also a prominent nationalist leader, and a founding member of the All India Muslim League, a member of the Hindu Mahasabha, and also President of the Indian National Congress (1921) (Ajmal Khan Road is a prominent area in Delhi). Most importantly, Ajmal Khan also helped establish the Jamia Millia Islamia University, as he was unhappy with the political (pro-British) affiliations of the AMU. Siddiqui perhaps shared this larger vision of the South Asian polity, and scored a minor political point by naming the compounds after a prominent Indian nationalist leader.

After partition, Liaquat Ali Khan, the Prime Minister (PM) of Pakistan, requested Jawaharlal Nehru, the PM of India, to make the services of Siddiqui available to Pakistan to develop its scientific base[7]. Nehru agreed, and the scientist who had the deepest knowledge of the chemistry of reserpine moved out of Indian research to head the Pakistan CSIR in 1951. He greatly influenced the development of chemistry in Pakistan, was made a Fellow of the Royal Society, and died in 1994. He continued to work on various aspects of reserpine till the 1980s, but mainly on its basic chemistry. In the meantime, in India, Rustom Vakil published an extensive study on the use of reserpine in hypertension, and provided a huge impetus to cardiology, in India and worldwide, through his work[8]. It was soon noted, mainly in the West that the use of reserpine often caused severe depression as a side effect, and its use in hypertension has declined over the last two decades.

The neurobiology of reserpine

The primary use of reserpine in psychiatry would have passed unnoticed till the *New York Times* (*NYT*) ran a story about R. A. Hakim from Ahmedabad, who was using Ayurvedic medicines costing a few paise, to treat mental illness[9]. The paper had received an award at the Sixth Provincial Gujarat and Saurashtra Medical Conference in Baroda, which was being covered, rather surprisingly, by the *NYT*. Combined with electro-convulsive therapy (another recent innovation, during WWII), he reported a recovery rate of 80% in schizophrenia, a rate vastly superior to any of therapies available at that time. As the editorial in the *NYT* noted, '*Ayurvedic drugs, easily available in India, may be worth a thorough investigation in some Western institution for the mentally afflicted*'. Soon Nathan Kline published a trial of reserpine on schizophrenia, with excellent results[10]. Coming a few months after the reports by Delay and Deniker on chlorpromazine, this promised a revolution in psychiatry.

This paved the way for a merger of neuro-chemistry and psychopharmacology, and dissection of the entire biology of dopaminergic pathways, beginning with Carlsson's 1957 paper on the anti-reserpine effects of DOPA; and for the body of work that followed these experiments[11], Carlsson was awarded the Nobel Prize in 2001. This Nobel Prize, for the understanding of the biology of reserpine, had been preceded by the award in 1965 to Bein and Woodward for elucidating the structure of reserpine (the logical culmination of the effort initiated by Siddiqui in 1932).

Advances in cell-biology methods helped understand that reserpine blocked vesicular mono-amine transporters, thus preventing recycling of the catecholamines that were taken back into the presynaptic neuron through the cell-membrane transporters. Over time, this resulted in the depletion of presynaptic catecholamines as greater amounts were broken down. This decrease was thought to contribute to depression, while dopaminergic excess was thought to be the basis of excitement, hallucinations and delusions. This model of the catechola-

mine theory of depression, and the role of various drugs in producing or reversing reserpine-like actions, as formulated by Schildkraut[12] has provided the most investigated biological model in psychiatry. Though we now know that the model is perhaps simplistic, it has remained one of the basic tenets of modern biological psychiatry.

In contrast, although reserpine was used in NIMHANS by 1950, and anecdotal accounts of its use are common all over India, this was apparently so commonplace that it did not excite the doctors to write a paper. Unlike insulin coma or leucotomy (which originated in the 'West', and case series of which were reported from India in the 1930s, a few years after their invention), reserpine was not subjected to great levels of enquiry. Most astonishingly, while scores of clinical trials of reserpine were conducted in Japan, eastern and western Europe, the UK and both Americas between 1953 and 1960, there was not a single published evaluation of its use in India. Lack of attention to the link between the psyche and the brain thus had a lasting impact on research, and understanding of neurobiology in India.

Molecular actions of reserpine and related alkaloids: the unfolding contemporary science

Meanwhile, in cardiology, the use of reserpine was understood in great detail, and other drugs, based on better understanding of their action on autonomic synapses became the cornerstone of therapy. However, the links between cardiovascular disease and mood disorders have still not been well understood. Also, it became evident that the other alkaloids from rauwolfia acted on ion channels and not on vesicular transporters. Ajmaline is now known to act specifically on sodium channels, and affect the heart. Prolongation of the QT wave complex in the ECG by ajmaline, is thought to be an endophenotype for Brugada syndrome, a rare autosomal dominant form of ventricular fibrillation[13]. The syndrome is a frequent cause of sudden death in Asia, and the gene has been localized to a particular mutation in the SCN5A promoter region, and the at-risk haplotypes are the most common in Asian populations, pointing to a pharmaco-genomic interaction. Curiously, the plant is native to the region.

In addition, alstonine and serpentine, both found in *Rauwolffia* species, have profound effects on glutamate and serotonin action[14]. It is interesting to note that the next generation of anti-psychotics that have just entered research, have identified action at the glutamate/serotonin receptor complex as the target for a new class of anti-psychotics[15]. Contrary to earlier experience, the glutamate and serotonin receptors seem to physically interact with each other and produce a receptor complex that can be a target for new drugs[16,17].

Thus, the *R. serpentina* plant produces a range of alkaloids, some of which block the vesicular mono-amine transporter and are responsible for the major effect of catecholamine depletion. Others target ion-channels and may directly affect the receptor complexes. The manipulation of these biological processes has been at the centre of modern psychopharmacology, and may even guide us to drugs of the future.

Lost opportunities

The actions of these plant extracts were described in ancient texts in India. Modern empirical evidence as well as the initial chemistry also emerged from South Asia. However, the lack of intellectual support, and interactions, between the scientific community, and within psychiatry in the mid-20th century in India did not allow this impetus to surge ahead. The partition also caused disruption in the scientific milieu of the region. The researches of Sen and Bose, Chopra, Siddiqui and Hussain in the pre-independence era, and later, clinical observations of Hakim and others were not followed up. Academic psychiatry got pre-occupied with the post-colonialism and acculturation debates at one end, and administrative responses to provide care without increasing services ('low-cost models') at the other end. Thus, an in-depth bio-medical scientific model, which could have developed similar insights into neuro-biology, as was done in the West by close observation in institutional settings, was conspicuous by its absence.

Also, the pre-occupation of medicine in India with the somatic (hypertension as a disease and cardiology as a discipline) rather than the mental consequences of reserpine (depression and insanity as disease, and psychiatry as a discipline) reflects an intellectual wariness of the mental space of our people by the medical scientists. This attitude may be a residue of colonial attitude towards science itself, wherein the 'native' mind was thought to be somehow different, while the body was much the same[18]. For emerging medical professionals needing international acclaim and recognition, the soma, rather than the psyche, became a much easier route for success. Thus, while Vakil became renowned for the actions of reserpine on the heart, it was the work of Bein and Woodward on its chemistry, and of Kline, Schildkraut and Carlsson, who understood its effect on the mind and brain by exploring its relationship to depression and neurotransmission, that provided the launching pad for psychopharmacology.

Learning from history

Disorders of the brain and mind are likely to be the most complex, and advances in biology (like those that followed reserpine) hold the promise of quantum leaps in our understanding, and thus treatments of those diseases. The unity of genomics in all life forms, basic similarities in cell structure and function, and co-evolution and distribution of various interdependent biological processes within and across species by evolution helps us understand the complex web of life. Such advances will result in the development of new medicines. It is thus imperative that we engage in the world of biological approaches with as much attention and commitment, as we do to psychopathology, epidemiology and service delivery, in psychiatry.

A decade ago, a lively debate was engendered in response to an editorial in the *Lancet*[19], wherein many psychiatrists had reacted sharply to suggestions that psychiatry would be globally divided into a high-tech care in the affluent societies, and low-cost management (in the Third World) as modern pharmacotherapy was 'out of reach of most physicians'. As these critics pointed out, despite the cultural diversity, the basic biology is shared across the world, and that the inequality of healthcare between the developed and developing world was a cause for concern that required research into all areas of neuroscience, rather than debates about the nature of

the brain vs mind, or 'western' and 'traditional' science and society[20].

The history of reserpine, widely used in traditional medicine in India till very recently (the 'paglon ki dawa' was available in many village markets for a few paise in the 1950s) provides one such model. Serpentine, ajmaline and reserpine have been withdrawn from the market as they are too cheap to produce profit and no patents apply (since they were discovered in India). The scientific and technological spin-offs from these products include several Nobel prizes, and a multi-billion psychopharmacology industry. New drugs based upon principles already known about these plant-derived small molecules, are likely to be among the most expensive. Even to be able to provide adequate care, at reasonable cost, it is necessary that scientists and psychiatrists learn from the wisdom of the plants, and the traditional knowledge around us, through the prism of modern chemistry and biology. Or else, we may never have affordable drugs, and equally importantly, lose opportunities to understand the interface between the natural world, and the brain and mind.

1. Avity, Pierre d', sieur de Montmartin, 1573–1635, *The Estates, Empires and Principalities of the World*, Transl: Edward, Adam Islip, London, 1615.
2. Paré, Ambroise, 1519?–1590. *The Works of That Famous Chirugion Ambrose Parey*, Trans: Johnson, T. Gates, London, 1637.
3. Peachie, John, *Of the Vertues of Cassummuniar*, Tho. Parkhurst, London, 1679.
4. Somers, K., *Med. Hist.*, 1958, **2**, 87–91.
5. Siddiqui, S. and Siddiqui, R. H., *J. Indian Chem. Soc.*, 1931, **8**, 667–680; *J. Indian Chem. Soc.*, 1932, **9**, 539; 1935, **12**, 37.
6. Alavi, S., *Loss and Recovery of an Indo-Muslim Medical Tradition, 1600–1900*, Permanent Black, Ranikhet, 2008.
7. Akhtar, M., *Biogr. Mem. Fellows R. Soc.*, 1996, **42**, 401–417.
8. Isharwal, S. and Gupta, S., *Tex. Heart Inst. J.*, 2006, **33**, 161–170.
9. Editorial, *New York Times*, 31 May 1953.
10. Kline, N. S., *Ann. NY Acad. Sci.*, 1954, **59**, 107–132.
11. Foley, P., *J. Neural Trans. Suppl.*, 2007, **72**, 5–15.
12. Schildkraut, J. J., *Am. J. Psychiatr.*, 1965, **122**, 509–522.
13. Brugada, J., Brugada, P. and Brugada, R., *Eur. Heart J.*, 2003, **24**, 1085–1086.
14. Elisabetsky, E. and Costa-Campos, L., *Evid. Based Complement. Altern. Med.*, 2006, **3**, 39–48.
15. de Moura Linck, V., Herrmann, A. P., Goerck, G. C., Iwu, M. M., Okunji, C. O., Leal, M. B. and Elisabetsky, E., *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 2008, **32**, 1449–1452.
16. Snyder, E. M. and Murphy, M. R., *Nature Rev. Drug Discov.*, 2008, **7**, 471–472. Epub 16 May 2008.
17. Weinberger, D. R., *Nature Med.*, 2007, **13**, 1018–1019.
18. Jain, S. and Sarin, A., *Natl. Med. J. India*, 2000, **13**, 329–330.
19. Editorial, *Lancet*, 1997, **349**, 965.
20. Jones, I., Craddock, N.; Pincus, H. A.; Forshall, S. and Sandford, J., *Lancet*, 1997, **349**, 1550.

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