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Special Opinion Paper

Indian *Rauwolfia* research led to the evolution of neuropsychopharmacology & the 2000 Nobel Prize (Part II)

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Between 1930 and 1950, a large number of Indian scientists had utilized the investigating systems of modern medicines to study scientifically an old herbal drug *Rauwolfia serpentina* used for centuries in folk medicine for a variety of illnesses, which included mental illness. Thus, chemical, pharmacological and therapeutic investigations were carried out on various alkaloids extracted primarily from the roots of this plant. The Indian Research Foundation Association (IRFA), fore runner of the Indian Council of Medical Research, (ICMR) established an 'Indigenous Drugs Inquiry' under (Lt-Col) R.N. Chopra at the School of Tropical Medicine at Calcutta (now Kolkata). He along with other colleagues studied the pharmacology of the various alkaloids extracted from the *Rauwolfia* plant obtained from different parts of the country. Their first paper was published in 1933[1]. Before this, Sen and Bose[2] and Siddiqui and Siddiqui[3,4] had isolated a number of alkaloids and characterized their chemistry. They continued their studies on alkaloids of *Rauwolfia* up to 1939[5]. The renowned chemist Ray, wrote about the hypnotic effect of *Rauwolfia* in 1931[6].

Chopra and colleagues[7-9] contributed a large number of studies on the pharmacology of various alkaloids of *R. serpentina*. From the same group, Gupta *et al*[10-12] and Dutta and Gupta[13] reported the physiological and the therapeutic effects of these alkaloids. Several other investigators continued these investigations[14-17]. It is interesting that even after 1955 when Brodie *et al*[18-23] took up the detailed study of these alkaloids, a number of Indian scientists continued to contribute to this field[24-31]. Chopra and Dandiya[32] and Bapna and Dandiya[33] were among some of these. K.P. Bhargava from the same department where B.B. Bhatia in 1940 did pioneering work on *R. serpentina*, went of to University of Utah, School of Medicine, USA, in 1955 and worked with H.L. Borison on the effect of *Rauwolfia* on central-evoked vasopressor responses[34,35]. Thus, by the early 1950s, it had been firmly established that some of the alkaloids of *R. serpentina* have sedative and antihypertensive effects. There was some evidence of their usefulness in treating mental disorders. A paper by Vakil[36] from Bombay (Mumbai) in 1949 about the role of *Rauwolfia* alkaloids in the treatment of high blood pressure and a news item in New York Times in 1953, about their use for successfully treating psychotic patients by Hakim from Ahmedabad attracted the attention of Bernard Brodie, Chief of Chemical Pharmacology, at the National Heart Institute, National Institute of Health (NIH), and N.S. Kline of Columbia University, New York[37]. Around the same time, Ciba Laboratories (now Novartis) in Switzerland published the first complete report on chemistry and pharmacology of reserpine which was

isolated in 1952 and introduced as the drug *Serpasil*[38]. Since, at that time, no reliable treatment was available for mental disorder and psychosis or high blood pressure, there was a widespread interest in research on *Rauwolfia* alkaloids especially reserpine both by the clinicians and the basic scientists, especially pharmacologists, all over the world. It may be mentioned that chlorpromazine was introduced a couple of years before the awareness of *Rauwolfia* outside India. Reports on the subjects soon appeared from the USA, UK, New Zealand, Germany, Austria, Switzerland and Japan[39]. According to Vakil, one company in India claimed to have sold 94 million tablets of the dried root in 1954 and it was exported to 17 countries throughout the world[40].

Attempts are made here to summarize some of the important contributions which ultimately led to the evolution of the field of neuropsychopharmacology and development of some of the drugs for the treatment of mental disorders, especially depression. Some of these studies provided initial evidence on the role of dopamine in the aetiopathogenesis of Parkinson's disease. Even more important, they established the role of chemical transmission in the central nervous system which opened a vast new field of neuropsychopharmacology.

Beginning of neuropsychopharmacology was initiated by constructing a spectrophotofluorometer in Brodie's laboratory in the early 1950s. It was also the beginning of pharmacological studies on the antipsychotic effect of reserpine and chlorpromazine. The seminal discovery that led to the understanding of reserpine's mode of action came from Bernard Brodie's laboratory at the NIH. Brodie and Shore[22] examined serotonin (which was discovered in mammalian brain in 1953) and reserpine which was introduced in the USA around the same time and found that both compounds potentiated hexobarbital-induced sleep and both were antagonized by lysergic acid diethylamide (LSD)[18,40]. This promoted them to speculate that reserpine worked through an action on serotonin. Brodie *et al*[19] reported that reserpine reduced serotonin levels in the brain and produced sedation. Pletscher *et al*[41] reiterated serotonin release as a possible mechanism of reserpine action. Two years later, Brodie and Shore (1957)[22] proposed a concept for a role of serotonin and norepinephrine as a chemical mediator in the brain and hypothesized that this explains the actions of the tranquilizing agents reserpine and chlorpromazine and the hallucinogenic agent LSD and muscaline.

Around this time, Carlsson *et al*[42,43] from Sweden joined Brodie's laboratory on a sabbatical. He along with Shore and Brodie established release of serotonin from blood platelets *in vitro* (and this by reserpine). This was limited to alkaloids that exerted tranquilizing effects in animals[42-44]. In contrast, chlorpromazine, lysergic acid and phenobarbitone did not release serotonin. Shore *et al*[45] had already shown that reserpine releases serotonin from various body depots, including intestine and brain. It was interesting that Chopra *et al*[8] had earlier established that the sedative and hypnotic properties of *Rauwolfia* alkaloids were present mainly in alcohol extracts and the total alkaloids were free of ajmaline, serpentine and serotonin.

It was discovered that reserpine caused prolonged depletion of serotonin from the brain and that the time course of serotonin depletion and recovery correlated with the pharmacological effects of reserpine, *e.g.* sedation[40.46]. They demonstrated that like chlorpromazine, reserpine also potentiates the tranquilizing effects of hexobarbitone and ethanol[18,19,21,40,45]. Thus, the action of reserpine appeared to bear a temporal relationship to the change in the brain serotonin rather than the concentration of reserpine[22]. The free amine (serotonin) released by reserpine was found to be unevenly distributed in the brain; its concentration was highest in the brainstem, specially the hypothalamus, and lowest in the cortex. Reserpine was found to act on the brainstem, apparently through free serotonin. Noce *et al*[47] found that reserpine exerted its hypotensive and sedative effect through its action on hypothalamus.

Bhargava and Borison[34] independently investigated the effect of *Rauwolfia* alkaloids on hypothalamus, medullary and spinal vasoregulatory system. They reported that the site of hypotensive action of *Rauwolfia* alkaloids, which had commonly been claimed to be hypothalamus by Bein *et al*[48], was medullary centres. They found that in decerebrate animals, in the absence of hypothalamus, *Rauwolfia* was still capable of producing its hypotensive action[34]. In another paper, Bhargava and Borison[35] compared the effects of various *Rauwolfia* alkaloids on centrally evoked vasopressor responses. The results indicated that the alkaloids rescinnamine and reserpine are to be classed with reserpine because of their mildly depressant effect on the electrically induced medullary pressor responses. Similarly, the alkaloids serpentine and ajmaline can be classed with alseroxylon because of their primary depressant effect on medullary pressor responses[35].

After returning to Sweden from Brodie's laboratry, Carlsson, along with Hillarp[49], initiated their studies on the effect of reserpine on catechotamines. They soon discovered the depletion of adrenal medullary hormones as well as noradrenaline catecholamines store by reserpine in other tissues including brain. Shortly afterwards, Carlsson along with his students Bertler and Rosengren demonstrated depletion of noradrenalin stores in the heart and brain[50]. They also showed that the sympathetic nerves ceased to respond to stimulation following depletion of catecholamines by reserpine[43-45,50]. Holzbauer and Vogt[51] reported depression of noradrenaline concentration in the hypothalamus of cats by reserpine.

In 1959, Carlsson demonstrated that administration of reserpine to rabbits caused almost complete depletion of both dopamine and noradrenaline from the brain[52]. He considered this to be responsible for this tranquilizing effect of reserpine. Injection of 3-4 dihydroxyphenylalanine (DOPA) to the normal and reserpine treated rabbits caused marked increase in the level of dopamine in the brain[52]. His students demonstrated that while the highest concentration of noradrenaline was in the brainstem probably hypothalamus, practically all dopamine occurred in the corpus striatum[53,54]. He proposed that the Parkinson's syndrome observed after treatment with reserpine was due to its action on depletion of dopamine from the corpus striatum. Carlsson *et al*[55] expressed his happiness on these observations, "We were pleased to find that dopamine did accumulate in the brain of animal treated with DOPA following reserpine pretreatment". Around the same time, Ehringer and Hornykiewicz[56] discovered low levels of dopamine in the basal ganglia of Parkinson' disease patients and demonstrated therapeutic effects of L-DOPA in Parkinson's patients[56,57]. Carlsson regretted having 'to disagree with my highly esteemed mentors and friends Drs Brodie and Shore'. They concluded that not only 5-hydroxytryptamine (5HT) but also the catecholamines had to be considered in attempts to explain the mode of action of reserpine.

Further studies on the action of 3,4-DOPA and 5HT and catecholamineine precursor DOPA on reserpinized animals by Carlsson *et al*, 1957[44] suggested that lack of catecholamines rather than 5HT (serotonin) was responsible for the gross behavioral actions of reserpine. They showed that the administration of DOPA to reserpine treated animals reversed the drug-induced effects[44,50]. Not only the above findings enhanced our understanding of the mechanism of action of reserpine on the central nervous system, according to Rubin (2007)[58], these also laid the ground work for other investigators to examine the action of diverse drugs on the brain amines. This was considered as one of the most important findings in pharmacology up to that time[59].

It was interesting that Anand *et al*[25] using implanted electrodes in the hypothalamus, demonstrated that reserpine not only depressed sympathetic centres in the diencephalon but also facilitated the parasympathetic centres, thus confirming the biochemical findings of Holzbauer and Vogt[51]. Malhotra and Pundlik[26] investigated the effect of reserpine on the acetylcholine content in the different areas of the central nervous system of the dog. They found an increase in the acctylcholitic content of all areas of the brain, except hippocampus following administration of reserpine. These findings were considered to be of major significance, since these provided convincing evidence accumulated by Carlsson *et al*[60] of information on chemical neurotransmission in the central nervous system. It is surprising that some of the most prominent pharmacologists of the time including Sir Henry Dale, Sir John Henry Daddum, and W.D. Paton were very skeptical about a link between the biogenic amines and brain function[58]. As a matter of fact, Sir Henry Dale pronounced that L-DOPA was a poison[60]. As a matter of fact McLennan in his book Synaptic Transmission stated, 'There was no evidence favouring chemicals transmission in the central nervous system'[61]. Undettered by such opposition, Carlsson continued to collect evidence about the existence of chemicals transmission in the central nervous system.

Anden *et al*[62] demonstrated that besides the well known depletion of serotonin, noradrenaline and dopamine in the brain, reserpine also caused changes in the concentration of certain monoamine metabolites in the brain. Along with Hillarp, Carlsson at Göteborg developed the technique of histoflourescence for estimating various monoamines in various regions of the brain[63,64]. The neuronal localization of the central monoamines was confirmed by lesion experiments. This demonstrated the disappearance of dopamine from the rat neostriatum following a lesion in the substantia nigra[63]. Moreover, removal of the striatum resulted in accumulation of dopamine in the substantia nigra. Carlsson *et al*[63,64] made important contributions regarding monoamine metabolism in the brain which was contrary to the prevailing views. This included

action of reserpine. It was observed that chlorpromazine and haloperidol had reserpine like action but lacked the monoamine-depleting properties of reserpine.

It was the result of these studies on the effect of reserpine on brain monoamines that led to the monoamine theory[65-67]. These studies led to other investigations on the search of causes of mental disorders, particularly depression. Thus, in 1965, Schildkraut of Harvard University proposed that depression stems from a deficiency of norepinephrine[68]. Holzbauer and Vogt[51] demonstrated that reserpine caused depression of noradrenaline concentration in the hypothalamus of the cat. The monoamine hypothesis was found to explain the depressogenic mechanism, reserpine being different from other depresogens. A detailed discussion on the subject was provided by Baumeister *et al*[65]. The monoamine hypothesis arising out of reserpine-related studies (pharmacological and clinical) led to the biochemical theories of mental disorders, thus stimulating biological psychiatry, introducing paradigm shift in brain research, in general, and psychiatry, in particular[65,69].

The concept of chemical transmission made it possible to clarify the mode of action of numerous drugs on the central nervous system. These results became the starting point for the much debated dopamine hypothesis of schizophrenia[69].

It may be interesting to quote Baumeister *et al*[65] from the department of Psychology, Louisiana State University, in this connection, "Prior to the psychopharmacology revolution of the 1950s and 60s, psychiatry had a bad reputation due to the use of crude ineffective and sometimes barbaric treatments… The biochemical theories of mental disorders and the related drug therapies that evolved during the 50s and 60s helped to establish psychiatry as a 'real' medical discipline … it supported the development of paradigm shift in psychiatry away from psycho-analytic explanations and archaic somatic treatments towards biochemical explanations and pharmacotherapy for mental disorders"[65]. While most others like, those in India as well as Bernard Brodie, Nathan Kline, Martha Vogt, N.E. Anden lost their interest in research in this field, Carlsson continued it even after receiving the Nobel Prize in 2000[70]. He indicated that "our subsequent work on chlorpromazine and other antipsychotic agents led us to propose that these agents act by blocking receptors for dopamine and partly for receptors for noradrenaline and serotonin"[69]. His interest in the drugs in mental disorders led him to discover that many antidepressants could also block the reuptake of serotonin which led his group to develop a compound that selectively blocked the reuptake of serotonin without acting on noradrenaline. The first such agent, known as selective serotonin reuptake inhibitors (SSRIs) was zimeldine. Though it was soon withdrawn due to very rare but serious side effect, several other SSRIs like prozac were developed soon[71].

The seminal discovery that led to understand reserpine's mode of action arose from Bernard Brodie's laboratory. His group established that the prolonged pharmacologic effect of reserpine was mediated by the persistent release of serotonin. The action of reserpine appeared to bear a temporal relationship to the changes in the brain serotonin rather than to the concentration of reserpine[18-23]. Subsequently, Carlsson, who started studies on pharmacology of reserpine in Brodie's laboratory, and continued these for many years in his laboratories in Sweden, along with a number of colleagues and students, demonstrated that besides serotonin reserpine affected monoamine concentration also.

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