HIGHLIGHTS OF PHARMACOL IN INDIA[1]

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Prior to 1922, pharmacology as a distinct scientific discipline did not exist in India. In 1921 the Calcutta School of Tropical Medicine was started, and for the first time a full chair on pharmacology was established. The duties of the chair included, among others, the study of pharmacology of Indian indigenous drugs claimed to be efficacious in the treatment of various tropical diseases. Professor Ram Nath Chopra, a student of Professor Walter E. Dixon of Cambridge, was selected as the first professor. He initiated, along with Hugh W. Acton, Director of the school at that time, systematic studies in experimental pharmacology as a postgraduate and research discipline in this Institute. Trends in medical education were fast changing in India, and soon pharmacology was recognized as an essential part of the teaching discipline in the medical colleges in place of the old and time-honored descriptive materia medica.

From about 1925 to the beginning of 1940, there was hardly any highlight in pharmacological teaching and research in India except in the two post-graduate research centers at the School of Tropical Medicine, Calcutta, and the Haffkine Institute, Bombay. Even at these two centers, beyond the routine screening of indigenous drugs, almost no detailed experimental, analytical, or biochemical pharmacology was attempted.

During World War II, India was in the grip of drug "famine" as a result of the almost complete cutting off of supplies from Europe and other countries. This focused the attention of the administrators on the pharmacologists who were in teaching and research institutions in the country, and they were charged with the procurement, production, and development of drugs urgently needed for the theaters of war in the Southeast Asia and Pacific regions. The importance of pharmacology for the first time came into prominence, and it is creditable that at this time the Indian pharmacologists, though ill-equipped and without proper paraphernalia, rose to the occasion and, with the help of chemists and pharmacists, developed substitutes and indigenous replacements for many of the drugs commonly used in the treatment of war injuries and for the prevention of such conditions as cholera, smallpox, and other diseases. The war, therefore, can be considered to have played a very important part in the development of pharmacologic teaching and research and in the progress and development of the pharmaceutical industry.

Early Pharmacological Studies

As has been already mentioned, the major interest of pharmacologists in India had been the screening of the age-old remedies known to the ancient

[1] The survey of the literature pertaining to this review was concluded in May 1961.

system of medicine in the country and to find out from these whether the claims advanced for them by the practitioners of ancient medicines were true. The work at the School of Tropical Medicine and at the Haffkine Institute, therefore, was initiated with the following main objectives in view: (*a*) To make India self-supporting by enabling her to utilize the drugs produced in the country, by manufacturing them in a form suitable for administration. (*b*) To discover remedies from the claims of Ayurvedic, Tibbi, and other indigenous sources suitable to be employed by the exponents of western medicine. (*c*) To discover the means of effecting economy, so that these remedies might fall within the means of the great masses in India whose economic condition is very low. (*d*) Eventually to prepare an Indian Pharmacopoeia.

During a period of about 30 years, much work in this field has been done. Many important medicinal plants of the ancient Hindu materia medica have been carefully investigated from every point of view. Their chemical composition has been determined, the pharmacological action of the active principles worked out on animal experiments, and suitable preparations have been tested on the patients in the hospitals. It is only by a thorough inquiry that the real merits of these drugs can be proved and a demand created for them not only in India but in other parts of the world. This laborious work has brought into prominence the merits and qualities of certain drugs (1), e.g., *Holarrheana anti-dysenterica*, *Rauwolfia serpentina*, *Butea frondosa*, *Alstonia scholaris*, *Caesalpinia bonducella*, *Adhatoda vasica*, *Bacopa herba*, *Daemia extensa*, *Cissampelos pareira*, *Terminalia arjuna*, *Psoralea corylifolia*, *Sida cordifolia*, *Swertia chirata*, *Andrographis paniculata*, *Plantago ovata*, *Thevetia neriifolia*, *Rivea cuneata*, etc., and it has been shown that they may prove to be valuable additions to the present armamentarium of the medical man to relieve the sufferings of humanity, if brought into general use. Such drugs, unfortunately, are not many. A large number of those examined showed a certain amount of activity but were not found to be superior to the drugs already occurring in the Pharmacopoeias of Western countries; in fact, they were not even nearly as efficacious. A third group of these drugs consists of those remedies which although largely used in indigenous medicine were found to have little or no activity whatever. Many drugs of questionable value and doubtful utility crept into the indigenous systems. Full details of work done in this connection have been published in such books as *The Indigenous Drugs of India* by Chopra (2) and *Indian Pharmaceutical Codex* by Mukerji (3). A full list of all the drugs tried or under examination is available in *Glossary of Indian Medical Plants* by Nayar (4).

Cardiovascular Pharmacology

Two new glycosides, peruvoside and ruvoside, isolated from *T. neriifolia* have been shown by Kohli, Vohra & De (5) to be potent cardinolides. Peruvoside may be a clinically useful glycoside with quick action, good oral

absorbability, and reasonable duration of action. Ruvoside, on the other hand, may offer no advantage over the other short-acting glycosides as it is poorly absorbed orally and has a rather short duration of action (6). Thevetin "A", the parent glycoside of peruvoside series which has properties similar to thevetin [studied earlier by Chopra & Mukerji (8)], has also been studied from a comparative angle by De and colleagues (7).

Arora and his colleagues have shown that antiveratrinic and antiarrhythmic activities are almost always present together and that no specific chemical structure was required for the antiveratrinic activity (9, 10). There was, however, no quantitative relationship among these properties, although antiarrhythmic activity against auricular arrhythmias may bear some correlation with antiveratrinic activity (11). Recently, a series of coumarins have been shown to possess antiveratrinic activity, and a few compounds among these may possess promising antiarrhythmic activity (12).

Several groups of drugs have been shown to possess antiarrhythmic activity by employing conventional techniques for producing experimental arrhythmias. A number of antimalarials (13 to 16) have been screened and some of these have been found to be more potent than quinidine. A few antimalarials have also been studied for effects on heart rate and conduction system (17, 18). Quinoline ring was found to be essential for negative inotropic activity in these compounds which also possessed anticholinergic activity (19). Ataractics (20), anticonvulsants (21), and antihistaminics (22) have all been found to possess marked antiarrhythmic activity. Bose and colleagues have shown that antimalarials and anticonvulsants reduced the acetylcholine content of the heart and brain (23, 24).

These studies have brought forward additional evidence in support of the concept that chemically diverse but pharmacologically homogenous groups may possess all the components of the pharmacological action. Thus, for instance, it has been shown that all antimalarials have both antiveratrinic and antiarrhythmic activities. This observation has been extended further with regard to musculotropic (25) and local anesthetic activity (26) among antimalarials, these two properties being a part of the pharmacological syndrome of quinine.

Two indigenous drugs have also been shown to possess promising antiarrhythmic activity. Jatamansone, a pure ketonic principle isolated from the essential oil of *Nardostachys jatamansi* has been shown to possess tranquilizing and antiarrhythmic activity (27). General pharmacological and toxicological investigations have shown this material to be a safe therapeutic agent (28). The other substance is the volatile oil of *Acorus calamus* which also possesses tranquilizing and promising antiarrhythmic activity besides antivaratrinic and anticonvulsant activity (29). Special advantage of these substances is their tranquilizing activity which will allay the anxiety associated with cardiac arrhythmias. A new steroid anesthetic hydroxydione has recently been shown to possess antiarrhythmic activity (30). Das & Arora

(31) have also studied the effects of barbiturates and autonomic agents on automaticity of the sino-auricular and auriculo-ventricular nodes.

Rauwolscine, a major hypotensive alkaloid of *Rauwolfia canescens*, has been the subject of a number of studies. Kohli *et al.* (32) showed that its adrenergic blocking activity was 2½ to three times stronger than tolazoline (Priscoline). It was also shown to possess nonspecific spasmolytic, local anesthetic, and aphrodisiac activity (33, 34). It produces central stimulation followed by depression (35). The hypotensive action of the alkaloid has also been studied to indicate the role of central action in its vasodepressor effect (36, 37). A large number of other studies concerned with Rauwolfia alkaloids have been reported. These have been recently reviewed by Kohli & Mukerji (38).

Interest has been taken in investigating central action of a series of hypotensive agents which are known to have a major peripheral site of action, e.g., ganglion blocking agents and adrenergic blocking agents. Bhargava (39) employed such methods which would permit the assessment of central action independent of the peripheral action, such as injection into the vertebral arteries, injection into the lateral ventricles, and introduction of the drug into isolated cerebral circulation. Effect on carotid occulsion pressor response, pressor and depressor responses elicited by central stimulation of the cut vagus, direct electrical stimulation of vasomotor centers by Horsley-Clark Stereotaxic technique, and spinal compression vasomotor response (SCVR) were used as the parameters. Afferent vagal stimulation has been considered a better response than carotid occlusion (40). Bhargava & Kulshreshtha (41, 42) studied the effect of various drugs on SCVR and stressed the significance of this response.

By employing this analytical approach, Bhargava & Dhawan (43, 44) have shown that, among the ganglion-blocking agents tested, pempidine has central vasomotor stimulant action; mecamylamine, hexamethonium, and tetraethylammonium have a central depressant action, and pentolinium and chlorisondamine have been found to be devoid of any central action.

All the adrenergic blocking agents studied were shown to have additional central hypotensive action (45). Hydralazine and chlorpromazine have also been shown to have definite central vasodepressor action (46, 47). The latter appears to be acting on the hypothalamic region.

Drugs Acting on Central and Peripheral Nervous System

In the course of an investigation on the synthesis of central stimulants a series of phenyl propionic acid esters and corresponding alcohols have been tested for central nervous system (CNS) activity by Kapil *et al.* (48). Among these compounds, 2-piperidyl-(1)-3 phenyl propanol was found to be the most active, producing increased purposeful CNS activity in different species.

Gujral and colleagues (49, 50) have discovered hypnotic activity in a new series of compounds, namely, 2-3-disubstituted quinazolones. They have further shown anticonvulsant and antipyretic activity in these compounds

(51). Among these 2-methyl-3-orthotolyl-4-quinazolone was found to be more active than phenobarbital (phenobarbitone), and a dependable hypnotic effect was noted in preliminary clinical trials (52). Sareen *et al.* (53) have studied the structure activity relationship of various derivatives of quinazole-4-ones. 3-phenyl-quinazole-4-one was shown to be essential for CNS depressant activity. Various truncated portions of this moiety were shown to be devoid of any such activity. General pharmacological action and toxicity of the 2-methyl-3-orthotolyl-4-quinazolone has recently been studied, and hypotensive, local anesthetic, and spasmolytic activity have also been demonstrated (54).

Having noted that anticonvulsants possessed antiarrhythmic activity, Arora & Kapila (55) tested several antiarrhythmic compounds for the anticonvulsant activity. The results have been variable, but the studies have in a way lent further support to the unitarian concept of nerve and muscle impulse. Mukherjee & Chakravarthy (56) have investigated the nature of anticonvulsant action of bromides and correlated it to intracellular electrolytes. Bose *et al.* (57) have shown that anticonvulsants produce reduction in serum albunin and a rise of globulins in the blood.

Dhawan and co-workers (58, 59) have studied the interaction of lysergic acid diethylamide (LSD-25) with various drugs. A specific antagonism has been shown to exist between LSD-25 and morphine and related drugs (60, 61, 62). Gupta & Dhawan (63, 64) have evaluated effect of drugs on reserpine emesis in pigeons. The emesis is prevented by LSD-25, caffeine, iproniazid, methamphetamine, morphine, rauwolscine, and yohimbine. Parallelism exists between the ability of a drug to block this emesis and its other anti-reserpine effects.

Following the success with Rauwolfia, a number of plants have been studied for ataractic activity with encouraging results, e.g., *Nardostachys jatamansi* (65 to 68), *Acorus calamus* (69, 70), *Wythania somnifera* (71, 72), *W. ashwagandha* (73), etc. *Herpestis monniera* has been shown to potentiate hypnotic effect of barbiturates and alcohol (74, 75, 76). A related plant, *Hydrocotyle asiatica*, which is known by the same vernacular name as *H. monniera* and reputed for similar properties, has been shown to have only weak sedative activity (77).

The quarternary salt of Hayatin, an alkaloid isolated from *Cissampelos pareira*, has been shown to be a potent neuromuscular blocking agent by Pradhan & De (78). Several other derivatives of this alkaloid (79, 80) and a number of synthetic bisonium compounds have been studied for neuromuscular blocking activity by Ray *et al.* (81 to 84) with interesting results regarding structure action relationship in this series.

Experimental Therapeutics

Antidiabetic drugs.—Antidiabetic drugs have interested several workers at different centers of research. One aspect of these studies has been the search for antidiabetic activity in indigenous drugs. As already, pointed out

a large number of plants have been attributed antidiabetic properties. The earlier work on these plants has been reviewed by Mukerji (85). Among the recent studies, the following plants have been investigated: *Vinca rosea* (86), *Pterocarpus marsupium* (87, 88), *Eugenia jambolina* (89), *Allium cepa*, *Lochnera rosea*, *Rivea cuneata* (90), *Ficus glomerata* (91), *Ficus bengalensis* (92), *Momordica chirantia* (93, 94), *Dolichos lablab*, *Phaseolus mungo* (95). The usual methods have been employed for studying antidiabetic action, e.g., the effect on blood sugar in fasting animals and on alloxan diabetic animals. In some cases partially pancreatectomized animals have also been used. Shrotri & Aiman (96) have given a critical review of the methods for studying antidiabetic activity. Among the plants studied most of them appear to possess hypoglycemic activty in normal animals but are not so effective in the absence of insulin.

The other aspect of antidiabetic research has been to study the mode of action of the oral antidiabetic compounds of the sulphonyl-urea series. According to Mukherjee *et al.* (97) carbutamide potentiates the action of insulin, whereas Aiman & Chowdhry (98) have suggested that it releases insulin from some bound form. It has, in any case, been shown to be ineffective in alloxan diabetes (99). Tolbutamide was shown to increase the effect of insulin both in intensity and duration (100). According to Bose *et al.* (101) tolbutamide acts by inhibiting the phosphokinase system, thus inhibiting the conversion of glycogen to glucose in the liver. Chlorpropamide, another new derivative, has also been shown to be insulinogenic (102).

Some new synthetic agents have also been studied for their antidiabetic property. Paul *et al.* (103) assumed that the antidiabetic activity of the sulphonyl ureas may reside in the thiourea moiety. They synthesized several hydantoin and hydantoic esters, and some of these were shown to have marked hypoglycemic activity (104). Some biguanide derivatives have also been synthesized for similar purpose by Basu *et al.* (105).

Atherosclerosis.—Chakravarti and colleagues (106, 107, 108) have been interested in the problem of atherosclerosis. The factors influencing the production of atherosclerosis and the effect of various dietary fats on atherogenesis were studied by these authors. Therapeutic studies with vitamins showed that vitamin B_{12} is more effective than ascorbic acid in preventing atherosclerosis (109). Alpha tocopherol was found to enhance atherogenesis. Desiccated thyroid and estrogen combination was found to be very effective in arresting the progress of the atherosclerotic process. Attempts are now being made to produce coronary occlusion and myocardial infarction in rats by use of steroid hormones (110).

Antiinflammatory drugs.—Among the plants studied for antiinflammatory properties, *Glycyrrhiza glabra* was found to have activity comparable to phenylbutazone (Butazolidine) or hydrocortisone. This activity has been attributed to glycyrrhizin the chief constituent of the plant (111). The antiinflammatory effect of glycyrrhizin is not mediated through adrenal

pituitary axis (112). Preparations containing gum-guggol obtained from the bark of *Balsamodendron mukul* have also been shown to possess marked antiinflammatory activity as tested against formalin arthritis (113). Fractions obtained from *Melia azadirachta* have also been shown to possess this property (114).

Peptic ulcer.—Experimental peptic ulcers, both acute and chronic have been produced by various methods in rats, guinea pigs, and dogs. Zaidi and colleagues (115, 116) have shown that mucus plays a significant role in the prevention and healing of experimental peptic ulceration. Some of the mucus stimulating drugs and the anticholinergic drugs have been studied; calcium eugenate and other allied compounds were found to prevent ulceration (117).

Chemotherapy.—As in other fields, a large number of plant extracts and principles have been screened for antibacterial properties. The detailed reference to these studies will not be possible here, but it may be added that none of the plant materials has held any promise of a potent bactericide. A number of plant extracts have been screened for antitubercular activity *in vivo* but without any encouraging results (118).

For antimycobacterial activity a large number of monosubstituted diaminodiphenylsulphones, sulfides, and sulfoxides prepared by Anand *et al.* (119) have been screened *in vivo* in rats and guinea pigs. Among these *p*-ethylamino-, isobutylamino-, and isopropylamino-diphenylsulphone, *p*-ethylamino-*p'*-amino-*m'*-hydroxydiphenylsulphone, and *p*-methylamino-*p'*-aminodiphenylsulfoxide proved effective in experimental tuberculosis of guinea pigs (120, 121, 122) and murine leprosy; the main advantage over diaminodiphenylsulfone was their greatly reduced hemotoxicity. Of these, *p*-ethylamino- and *p*-isopropylamino-*p'*-aminodiphenylsulphone, and *p*-methylamino-*p'*-aminodiphenylsulfoxide proved effective in human leprosy as well (123). Anand and colleagues have also studied the metabolism of these active sulphones, sulfoxides, and sulfides (124, 125, 126). It has been found that these *p*-alkylamino-*p'*-amino compounds undergo a certain amount of dealkylation, and conjugation with glucuronic acid. Further, sulfides and sulfoxides suffer both oxidation and reduction, so that in either case a mixture of sulfide, sulfoxide, and sulphone occurred as metabolites in the urine. These compounds have been shown to be very strongly bound to the plasma proteins. Various thiosemicarbazides having different acyl groups in position 1 and their derivatives were tested *in vitro* against H 37 Rv strain of *Mycobacterium tuberculosis*. Only those having an allyl group in position 4 were found to be active (127).

Amebiasis is another field in which a large number of studies have been reported. Series of compounds comprising substituted diamines, modified cinchona bases, chelatable oxygenated quinolines, quinazolines, mannich bases of chromones, thiochromones,
amebicidal activity *in vitro* and in experimental amebiasis in rats (128, 129).

All these compounds have shown variable degree of activity but the following two compounds possess marked activity: 4-(*p*-chloroanilino)-6-methoxy-2-methyl-8-quinolinol and 4-(*p*-anisidino)-6-methoxy-2-methyl-8-quinolinol (130).

A number of open-chain diamines, imidazolidinethione, and homopiperazine analogues of diethylcarbamizine (Hetrazan) have been reported by Wadia *et al.* (131, 132) for screening against filariasis. Of these the homopiperazine analogue of diethylcarbamazine was found to be about half as active as diethylcarbamazine and also half as toxic.

Some work has also been reported by Chatterji *et al.* (133, 134) on antimetabolites of purines and pyrimidines amongst pyrimidopyrimidines and glycosides of deazapurines (imidiazopyridines). Among these 1-deaza-7-β-D-ribofuranosyl-purine has been found to have a high order of activity against Ranikhet disease virus in tissue culture, and against KB cell line in tissue culture.

Antifertility Drugs

Effect of cadmium on some selected vulnerable points in the reproductive mechanism of both sexes was studied by Kar and colleagues. The irreversible destruction of spermatogenic epithelium in testis seemed to be direct and not mediated through the pituitary (135, 136, 137). The endocrine portion of the testis recovered after an initial phase of atrophy. In prepuberal female rats cadmium chloride destroyed the ovarian follicles within 48 hours. But this effect was reversible (138). In adult females there was little reduction in fertility, but a significant percentage of ova failed to implant. On the other hand, 19-norsteroids induced total (but reversible) sterility in female rats through an inhibition of ovulation *vis-a-vis* pituitary luteinizing hormone release (139). Similarly, a compound synthesized from diethylstilbesterol and formaldehyde was shown by Dhar & Kar (140) to cause 90 per cent sterile matings in the female rats. A series of aromatic compounds inhibited the peripheral action of gonadotrophic hormone in the female rats. Of these chloroacetocatechol proved to be most active. Preliminary trials for antifertility effects of this compound led to encouraging results (141).

Considerable interest was aroused by the claim that 2, 6 dimethylhydroquinone (*meta* xylolhydroquinone) isolated from the oil of an indigenous plant, *Pisium sativum*, caused 50 per cent reduction of fertility in the human female. The compound was shown to possess antigonadotrophic, antiestrogenic, and antiprogestational properties as well, and was reported to be nontoxic with no adverse effects on blood count and blood pressure. A number of analogues of this compound were prepared and tested for antiestrogenic, antigonadotrophic, and antiprogestational activities (142).

Out of the several indigenous plants studied for possible antifertility effects in rats, *Mallotus phillippinensis* proved to be encouraging in preliminary trials (143). The active principle was subsequently identified as

rottlerin, and its antifertility effects could be imputed to a significant prolongation of diestrous stage (144, 145). Citrantin, a pyrone derivative isolated from *Citrus aurantium* was claimed to have antifertility properties by Ghosh, Mukherjee & Bannerji (146). However, according to Pincus this compound failed to inhibit ovulation, fertilization or implantation in rats (147).

An exhaustive list of antifertility plants has been drawn by Casey (148).

Miscellaneous

Groups of drugs have been taken up for screening for particular types of activity. Thus, for intsance, a number of drugs have been screened for antipyretic (149, 150), spasmolytic (151), antiinflammatory (152, 153), diuretic (154, 155), and oxytocic properties (156).

M. azadirachta has been the subject of a number of investigations. Nimbidin has been shown to possess antibacterial and antifungal activity (157). The most important studies, however, have been by Bhide *et al.* (158, 159, 160) who showed that sodium nimbidinate had a powerful diuretic action. The general pharmacological action of nimbidin has been reported by Gaitonde & Sheth (161).

Psoralin and isopsoralin, active principles of Babchi (*Psoralea corylifolia*) and a mixture of the two, in combination with ultraviolet irradiation were tried in a large number of patients suffering from vitiligo; regeneration of pigment in many cases was noted (162).

Makaradhwaja, a popular general tonic (mercuric sulphide), has been claimed in Ayurveda as a potent therapeutic agent. The drug, however, is insoluble and doubts were raised as to the mechanism of its action. Experiments designed to determine the solubility of this drug suggested that "Makaradhwaja" is soluble in biological systems and may be absorbed orally in quantities sufficiently small to inhibit certain enzyme systems without interfering with any of the vital functions of the body (163).

Among imidazolidine thiones synthesized and tested for antithyroid activity, 1-isopropyl imidazolidine thione has been found by Karkun & Anand (164) to have activity comparable to methimazole.

Anthihistaminics have been shown by Rajapurkar & Panjwani (165) to restore the hypertensive responses of epinephrine made hypotensive by adrenergic blocking agents.

A new method by indwelling cannula in pigeons has been described by Ojha (166) for measuring the effect on gastric secretion. A method has been evolved by Datta & Habbu (167) to produce cholera infection in experimental animals. Inoculation of suitably cultivated vibrios directly into the small intestine of infant rabbits produced symptoms similar to human infection.

From the above, it will be seen that modern scientific pharmacology, as distinguished from materia medica, is a discipline of comparatively recent

origin in India, limited to the second and third quarters of this century. In consideration of its youthfulness, the development of the field has been particularly rapid as a teaching discipline in the medical, pharmacy, dental, and veterinary colleges. The research aspect has not yet been properly emphasized as there are hardly any drug manufacturing firms in the country that are appreciative of or eager to sponsor pharmacology in their reaesrch and production establishments. Most of the support for pharmacological research has so far come from the state agencies and the universities. There is a growing appreciation of the role that pharmacology can play in the development, standardization, and use of new drugs for the prevention, alleviation, and cure of several diseases in the tropics. Many young scientists are taking up pharmacology as a career in view of the steadily increasing openings for fruitful employment in this field. In the next decade, it is hoped that this trend will grow more intensively and that Indian pharmacology will be able to make significant contributions to the world knowledge in this field.

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