term Reverse Pharmacology, currently coined and systematized, bear any relevance to the discovery of modern drugs? These are the questions which may provide answers to assist the shift in paradigm for the new drug discovery process.

Poisons and Experimental Pharmacology

The word ‘pharmacum’ means a medicine or drug; also a poison.6 The etymology is in new Latin, later in Italian farmaco, from Greek ἀ μάκον, a drug, whether healing or noxious, a potion spell, charm, a deadly drug, poison, dye, colour etc.7 It is surprising that the term pharmaco also meant poison in Greek. That indeed was quite an example of Greek “wisdom”! The word ‘poison’ dates to circa 1230, from old French puison “a drink”, later “a potion, poisonous drink” from Latin potionem; Potare meant to drink from the base po/pi-to drink.8 The closeness to Sanskrit ipba to drink is obvious. However, in Sanskrit the terms for medicine and poison were distinct – AaOYaiQa (Aushadhi) and ivaYa/Agad (Visha/Agaga) respectively.9 The roots of the Western therapeutics lie in Graeco-Roman medicine. As a consequence poisons and strong drugs have always interested scientists and early pharmacologists. Swain, had traced the origin of some of the adverse effects of modern drugs to these roots.10 Table 1 lists some of the poisons investigated for their mechanisms. That led to a new understanding in physiology and pharmacology. The quest for safer chemical derivatives of these “poisons” led to the burgeoning field of medicinal chemistry for synthetic modern drugs. Later, the further development of the structure-activity relationship led to innumerable “new drugs” of a “me too” nature, Ivan Illich, a social critic, calls this situation of too many prescription drugs as “paradoxical counterproductivity.”11 The book - African Ethnobotany-Poisons and Drugs - by Hans Dieter Neuwinger has covered more than 240 poisonous plants. In an interdisciplinary manner he has dealt with the poisonous plants used for hunting as well as for medical treatment in traditional African medicine.12 The relationship of Asian, African and South American poisons to the development of modern drugs has been a relatively less stressed. Hence roots of several modern drugs activities in Ayurvedic therapeutics often go unrecognized.

Rauwolfia serpentina to Modern Drugs

Rauwolfia serpentina, Benth, the snake root of India, was widely used...
before scientific studies showed its efficacy in hypertension and mental disorders. Gananath Sen and Kartik Bose were the first to show, in 1931, the antihypertensive effects of the plant. Later Rustom Jal Vakil, published his clinical studies with R. serpentina in hypertension in the British Heart Journal, after 18 years. R. serpentina given proper credit to the masterly clinical observations of side who won Nobel Prize, in the field of biogenic amines, failed to the attention in many scholarly reviews. Even those scientists experimental tool coupled with clinical observations has escaped drugs. This revolution in new drugs ushered in by reserpine as an antihypertensive drug – Serpasil ® (CIBA). But this major pharmacology by Bein and colleagues led to the first major globally Isolation of the active principle of the plant – reserpine – and its effects. The spin-offs of these pioneering observations led to a peptic ulcer etc besides its antihypertensive and tranquillising effects. The syndrome of unusual bedside adverse or beneficial effects with an eye to events suggest the need for meticulous recording and documenting as an anti-Parkinson drug from Mucuna pruriens. A double arrhythmias modern drugs

<table>
<thead>
<tr>
<th>Poison Source</th>
<th>Human/animal effect</th>
<th>Mechanism/Agonist</th>
<th>Modern drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curare tomentosum</td>
<td>Conscious paralysis</td>
<td>Neuromuscular block</td>
<td>Tubocurarine, pancuronium, gallamine, suxamethonium</td>
</tr>
<tr>
<td>Physostigma venenosum</td>
<td>Ordeal poison</td>
<td>Anticholinesterase</td>
<td>Neostigmine, Pyridostigmine, Edrophonium, Pilocarpine</td>
</tr>
<tr>
<td>Strychnos nux-vomica</td>
<td>Convulsive death</td>
<td>Glycinergic receptor</td>
<td></td>
</tr>
<tr>
<td>Atropa belladonna</td>
<td>Fatal poisoning</td>
<td>Cholinergic blockage</td>
<td>Scopolamine, Cyclopentolate, Istratropium</td>
</tr>
<tr>
<td>Melilotus alba</td>
<td>Bleeding disease</td>
<td>Anti-Vitamin K</td>
<td>Dicumarol warfarin 1. Noradrenaline agonists 2. and β antagonists</td>
</tr>
<tr>
<td>Claviceps purpurea</td>
<td>St. Anthony’s f</td>
<td>Vasocostricor</td>
<td>1. Noradrenalin 2. and β antagonists</td>
</tr>
<tr>
<td>Erythroxylon coca</td>
<td>Central Stimulant</td>
<td>Local anaesthetic</td>
<td>Procaine l-utacaine dibucaine lidocaaine</td>
</tr>
<tr>
<td>Bothrops jaraca</td>
<td>Viper poison</td>
<td>ACE inhibitor</td>
<td>Capotopril, Enalapril</td>
</tr>
</tbody>
</table>

Table 1: Poisons as roots of modern drugs

<table>
<thead>
<tr>
<th>R. serpentina</th>
<th>Mechanisms</th>
<th>Modern Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertension effect</td>
<td>Noradrenaline (NA)</td>
<td>Reserpine, guanethidine, catecholamines</td>
</tr>
<tr>
<td>Depression</td>
<td>Depletion of NA, S-HT</td>
<td>Impiramine, Amtriptilime, fluoxetine, sertraline, bupropion</td>
</tr>
<tr>
<td>Gynecomastia/ Galactorrhea</td>
<td>Dopamine Depletion Increase in prolactin</td>
<td>Bromocriptine, cafergo-line pergolide, destinoxin</td>
</tr>
<tr>
<td>Parkinsonism Syndrome</td>
<td>Dopamine depletion in corpus striation</td>
<td>L-dopa, carbidopa pramipexole</td>
</tr>
<tr>
<td>Hyperacidity &amp; peptic ulcer</td>
<td>Release of histamine</td>
<td>Cimetidine, ranitidine, brocurine, famotidine</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>Depletion of noradrena-line</td>
<td>Oxymetazoline, xylometazoline</td>
</tr>
</tbody>
</table>

ADVERSE EFFECTS OF α METHYLDOPA AND PROLACTIN

In 1969, a young hypertensive girl was observed to have galactorrhoea-amnorrorhoea with Parkinsonism. The syndrome was ascribed to hypothalamic depletion of caracholamines with special reference to dopamine, due to α methyl dopa therapy. At that time assays for human prolactin were not available. This clinical observation led to the proposal of dopaminergic inhibitory control of prolactin secretion. In 1981, eleven years later, there were two cases reported with α - methyl dopa with dose-response relationship with a prolactin increase and amenorrhea-galactorrhea due to dopamine-depletion. While studying the effects of bromocriptine in a patient with hyperprolactinemia with visual field defects, a serendipitous finding emerged. The reduction of prolactin levels was accompanied by normalization of visual fields. This was the first demonstration of medical management of prolactinoma, later confirmed and accepted globally. These events suggest the need for meticulous recording and documenting of unusual side effects with an eye to the potential of new drug development. Later Mucuna pruriens Bak was investigated for reducing chlorpromazine- included hyperprolactinemia in psychiatric patients and for therapeutic effects in Parkinson’s disease. Zandopa HP-200) was evolved as an anti-Parkinson drug from Mucuna pruriens. A double blind clinical and pharmacological study with Mucuna pruriens in Parkinson’s disease suggested advantage of L-Dopa in long term arrangement of Parkinson’s disease.

ANTIMALARIAL DRUGS OF NATURAL ORIGIN

Cinchona-the Peruvian bark - story illustrates the tale of centuries of missed opportunities. The first written record of the use of cinchona dates back to a book published in 1639. The first official mention of the plant was in the London Pharmacopeia in 1677. Despite the widespread use of the bark for malaria, it was as late as in 1820 that Pelletier and Caventou isolated quinine from the plant. Artemisia annua was used, in China since antiquity, as a fever remedy. But the artemisinine and derivative
were delayed by millennia. The chemical structure of quinine assisted the medicinal chemists in synthesizing a large series of 4-aminoquinolines. Chloroquine emerged as a dominant anti-malarial drug. The inordinate delay in the path from the bedside to bench and then from the bench back to the bedside is primarily due to the lack of an organized transdiscipline like Reverse Pharmacology.

Recently, we have investigated the plant *Nyctanthes arbor-tristis* Linn through reverse Pharmacology, for key treatment of malaria. It led to a clinical and parasitic cure in 92 (76.7%) out of 120 patients. In a further in depth study, disease-modifying activity was observed as clinical relief often preceded the parasite disappearance. There was an early and marked drop in TNF-α levels. The petroleum ether extract showed IC₅₀ of 25-50μ/ml against the chloroquine sensitive and resistant strains of *Plasmodium falciparum* in vitro. This plant could be a significant example of bedside to bench path for new anti-malarial drugs. Currently, the putative active molecules are being investigated. Table 3 lists some plants which have a potential for new antimalarial drugs.

### REVERSE PHARMACOLOGY FOR MODERN DRUGS

Reverse Pharmacology as a term has two nuances. The first is the path of pharmacology from the bedside observations to bench experiments. The second is the search of drug-like molecules (endogenous or extrinsic) which dock-in with new macromolecules discovered through genomics and proteomics. For the present discussion, we will focus on the first meaning of Reverse Pharmacology.

Reverse Pharmacology is a transdiscipline that is comprised of three stages: 1) Experiential hits-documentation in Observational Therapeutics and Pharmacoepidemiology; 2) Exploratory stage of *in vitro* and *in vivo* studies to develop these hits into leads and 3) Experimental and clinical state-of-the-art relevant scientific research to determine safety, efficacy and mechanisms of action of the candidate drug. The scope of Reverse Pharmacology is immense due to the vast field of bedside observations. Table 4 lists the serendipitous clinical observations which led to the development of novel therapeutic indications or modified molecules as new drugs. But there were inordinate gaps between the serendipity and research creativity. Reverse Pharmacology as an organized transdiscipline would fill up the gaps.

### REVERSE PHARMACOLOGY: A STRATEGY FOR NEW DRUG DISCOVERY

For the last three decades our research group, firstly at CIBA Research Centre and Podar Hospital and later at SPARC and MRC-KHS, has been engaged in evolving Reverse Pharmacology as a novel strategy for new drug discovery. This was followed up by CSIR-NMITLI projects for diabetes mellitus, arthritis, hepatitis and psoriasis. ICMR has granted the first Advanced Centre in Reverse Pharmacology to our Kasturba Health Society. The CSIR-NMITLI programme was quite successful. Several hits, leads and drug candidates have evolved over the last seven years. However, the pharmaceutical industry is still lukewarm in taking up this new paradigm for drug discovery. Only after some distinct globally successful products emerge the industry may wake up to this cost-effective path for new drug discovery. Ayurveda has a very rich pharmacopoeia. Reverse Pharmacology when coupled with Observational Therapeutics, Pharmacoepidemiology and Systems Biology would enhance and complement the new drug discovery process. The high cost of modern drugs may then, hopefully be reduced. The insights obtained in non-drug interventions also can reduce the out-of-control health care budgets.
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