

## CHAPTER XVIII

# PHARMACOLOGY AND PHARMACEUTICAL INDUSTRY

India followed the British tradition of teaching *Materia Medica* as a comparatively minor subject to medical students till about 1940. The School of Tropical Medicine in Kolkata had created a Chair of Professor in Pharmacology for Col. Sir Ram Nath Chopra in 1922. The drug famine during the World War II brought the importance of pharmacologists in prominence and several departments of *Materia Medica* were upgraded to departments of Pharmacology with full time Professor as the head.

The growth of Pharmacology was very rapid after 1950 with opening of new medical colleges and developing post-graduate facilities at several centres. This was followed in due course with new institutions of Pharmacy and Veterinary Medicine. National laboratories such as Central Drug Research Institute (CDRI), Lucknow and R&D units of Pharmaceutical Industry (e.g., CIBA Centre, or those of Hoechst, Ranbaxy, Reddy's etc.) have also aided the process. The growth was substantially helped by return of many pharmacologists trained abroad; provision of fellowships by agencies like the Rockefeller Foundation and WHO for training within the country and abroad; establishment of specialized units or centres of advanced research by ICMR, CSIR etc.; and by visiting Professors from abroad. Thus the visit of Prof. Lewis to Seth GS Medical College, Mumbai initiated the development of the first Clinical Pharmacology facility of the country. Constraint of space will not permit a

comprehensive review of the contributions made by Indian pharmacologists; only the major highlights have been summarised below.

### NEUROPHARMACOLOGY

Several centres of excellence exist in the country. The investigators have used a variety of non-rodent and rodent animal species and routes of drug administration ranging from micro-iontophoresis to systemic routes. The parameters have varied from action potential of single neuron or biochemical parameters of *in-vitro* brain tissue to gross behaviour in normal animals. In some studies ablation and/or electrical stimulation of specific loci/centres has been undertaken.

#### BASIC NEUROPHARMACOLOGICAL STUDIES:

*Catalepsy:* Acetylcholine, histamine, 5-HT, dopamine, GABA and prostaglandins have been shown to play a direct or modulating role in experimental drug induced catalepsy. A modulating role of 5-HT in Parkinsonism has been demonstrated.

*Stereotypy:* Stereotypy induced by amphetamine, apomorphine and other dopamine agonists and methylphenidate has been analysed in-depth in mouse, rat, mastomys, guinea pig and pigeon. Dopaminergic mechanism is more important in the mammalian species whereas non-dopaminergic mechanisms enjoy a major role in the pigeon.

*Aggressive Behaviour:* This behaviour is mainly modulated by dopaminergic (D2), adrenergic, serotonergic (5-HT<sub>2</sub> and 3) and histaminergic (H<sub>2</sub>) mechanisms. Dopamine has an excitatory and 5-HT an inhibitory role. GABA and peptidergic systems are also involved in clonidine-induced automutilation.

*Learning and Memory:* Role of 5-HT (specially 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors), dopamine, cholinergic (muscarinic) and NMDA receptors has been elucidated by utilizing a variety of experimental paradigms in rat and mouse, including experimental model of Alzheimer's disease.

*Blood Brain Barrier:* The regulatory role of histamine (H<sub>2</sub> receptors) and prostaglandins has been established. The most important observation is transitory opening of the barrier by intravenous bolus of hypertonic saline. This has important clinical utility for delivering those drugs to the brain which do not easily cross the blood brain barrier.

*Thermo-regulation:* Indian studies were the first to demonstrate the involvement of  $\alpha$ -adrenoceptor in thermo-regulation. Subsequent studies in several species (rat, rabbit, guinea pig, mastomys, and pigeon) have delineated the role of dopamine, histamine, opioid peptides, prostaglandins and histamine and species specificity of some of their effects. The receptor subtypes for dopamine, opioid peptides, 5-HT and histamine have been identified. The mechanism of LSD<sub>25</sub>-induced pyrexia has been analysed.

*Central Cardiovascular Control:* The regulation of blood pressure, heart rate and rhythm have been analysed to elucidate the role of various subtypes of adrenergic, cholinergic, 5-HT and opioid receptors and of nitric oxide. Their involvement in modulating the central cardiovascular effects of drugs has also been studied. Two important outcomes have been identification of the spinal cord and ventral medulla as important regulatory sites and targets for drug action.

*Analgesia:* The mechanism of action of narcotic analgesics and their neurotransmitter modulation has been studied. The involvement of opioid receptors, acetylcholine, dopamine, 5-HT (5HT<sub>1D</sub>)

#### THE INDIAN PHARMACEUTICAL INDUSTRY: A BIG GLOBAL PLAYER

**P**roducer of largest number (about 350) of bulk drugs by any single country in the world. Major global supplier of generic drugs, targeting towards 10% of US generic drug market.

About 250 units have their own R&D Units recognized by the Government of India.

and histamine (H<sub>1</sub>) has been demonstrated. Opioids, prostaglandins and 5-HT are involved in stress induced analgesia. Analgesia by electrical stimulation of pretecal nuclei (SPA) utilizes multi-transmitter pathways involving opioid peptides, nitric oxide, acetylcholine, dopamine and nor-epinephrine.

*Peripheral Markers:* High affinity binding sites for 5-HT and dopamine exist in platelets. The dopamine D<sub>2</sub> platelet receptor is valuable in monitoring progress and response to L-DOPA in the patients of Parkinsonism. Indian studies also highlight the utility of receptors for dopamine, Nitric Oxide (NO) on the polymorphonuclear leucocytes in patients of Parkinsonism, migraine, schizophrenia, depression and other CNS disorders.

*Other Studies:* Role of histamine H<sub>1</sub> and H<sub>2</sub> receptors and enkephalins in the CTZ and vomiting center has been analysed. LSD<sub>25</sub> was shown to have potent anti-emetic activity. Dependence to morphine, cannabis, methaqualone and benzodiazepines has been extensively studied. Isatin (deoxindole) has been proposed to be a novel and important endocoid biological modulator in anxiety and stress.

#### DEVELOPMENT OF NEW DRUGS:

The first major CNS active drug to be synthesized and evaluated in India was Methaqualone. Phase I study in normal volunteers was also done. Lack of familiarity with the patent procedures unfortunately led to its commercialization as a hypnotic by drug houses in UK and US. Subsequently, more coordinated R&D activity led to



Photo: H.Y. Mohan Ram

*Curcuma longa (haldi). The rhizome is the source of curcumin, the natural orange-yellow food colourant, with potential uses in myocardial ischaemia and treatment of cancers.*

the development and marketing of several CNS active drugs within the country. These include the antidepressants nitroxazepine (Sintamil®, CIBA) and centpropazine (CDRI); neuroleptic biriperone (centbutindole, CDRI); local anaesthetic bucricaine (centbucridine, CDRI; Centoblock® Themis); neuromuscular blocking agent chandonium iodide and standardized extract of neotropic *Bacopa monnieri* (CDRI; Memory Plus®, Nivaran). A metenkephalin analog (CDRI 82/205) is being developed as a potent analgesic.

#### NEW ANIMAL MODELS

CDRI has developed a CNS screen with a battery of simple *in-vivo* tests for various CNS activities. It has screened about 4000 plants, several thousand synthetic compounds and over 500 marine products. A protocol has been standardized to study effects on cognitive behaviour of the rhesus monkey. A primate model of anxiety has been developed using sub-convulsive doses of metrazol in the rhesus monkey. CDRI has standardized the use of mastomys (*Mastomys coucha*) a new similar model, especially for studies on thermo-regulation and stereotyped behaviour. CDRI has also developed a single test for compounds effective in grand mal or petit mal epilepsy. Elsewhere in the

country, a status epilepticus model has been evolved. Clonidine-induced automutilation has been developed as a model of clinical self-injury.

#### CARDIOVASCULAR PHARMACOLOGY

Besides the central cardiovascular control, other major areas include cardiac arrhythmias, ischaemic injury, atherosclerosis and thrombosis.

*Cardiac Arrhythmias:* Several models have been employed to define the role of adrenergic and cholinergic mechanisms. The ventricle has poor cholinergic innervation. Still the acetylcholine level falls further after vagotomy in all the species studied. The negative inotropic effect is exerted by inhibition of  $Ca^{++}$  channel activity. The classical anti-arrhythmic agents decrease norepinephrine release in the myocardium. The  $\beta$ -adrenoceptor antagonists are most effective in blocking experimental arrhythmias. Ajmaline has good anti-arrhythmic activity.

*Myocardial Ischaemia:* The injury has been produced by isoprenaline, coronary artery ligation and by ischaemia-reperfusion in several species. The role of  $Ca^{++}$  in injury and the salvaging effect of calcium channel blockers has been shown in the reperfusion model. Protection has also been obtained with desimipramine and cardioselective  $\alpha$ - and  $\beta$ -adrenoceptor blockers. Minoxidil protects by opening the potassium channels and acting as a  $\alpha_2$  agonist in the isoprenaline model. Natural products coleonol, curcumin and picroliv also afford protection, besides the calcium channel blockers and  $\beta$ -blockers. Deleterious effect of thromboxane and protection with low dose of aspirin has been shown. Iloprost protects by increasing NO release and decreasing release of cytotoxic mediators.

*Hyperlipidemia and Atherosclerosis:* CDRI has developed sensitive acute and chronic models of hyperlipidemia in several species of laboratory animals. A standardized fraction of Gugulipid from *Commiphora wightii* has been marketed (Guglip®, CIPLA) and some synthetic analogues are under clinical evaluation. Clinically, lipoprotein(a) has

been shown to have a potent atherothrombogenic effect. A large pool of tryptophan concealed in normal low density lipoproteins (LDL) is exposed on the aqueous surface of LDL in diabetic patients.

**Thrombosis:** Two new thrombogenic factors modulating aggregation of platelets have been isolated from the serum. One is a low molecular weight fibrinogen-derived peptide and the other a  $\beta$ -globin gene related protein. Neutrophils play a pivotal role in thrombosis. Cyclooxygenase inhibitors and NO releasing compounds afford protection. Gugulipid, curcumin and anti-implantation agent centchroman prevent platelet aggregation.

**New Animal Models:** A model of frostbite has been developed in rat. Good experimental models of atherosclerosis and myocardial infarction have been standardized in the rhesus monkey. In addition acute (constriction of aorta above renal arteries) and chronic (spontaneous) hypertension has been produced in the same species.

**Development of New Drugs:** Detailed pharmacology of cardenolide, peruvoside, from the apocynaceous plant, *Jhevetia neriifolis* was studied in India but the drug was commercialized in Germany. Asclepin is another potent and safe cardenolide. Gugulipid became the first Indian natural product to be licensed in Europe after being marketed in India.

## ENDOCRINOLOGY

The major activity in this area has been in the fields of reproductive biology and diabetes.

### REPRODUCTIVE BIOLOGY

The main interests have been in understanding the mechanism of action of clinically used contraceptives and in the development of novel contraceptives.

**Basic Studies:** The physiology of fallopian tubes, cervix and the uterus and their role in ovum transport, fertilization and peri- and post-implantation events has been studied. The steroidal contraceptives inhibit steroidogenesis, leading to suppression of hypothalmo-hypophyseal system



Photo: C.M. Gupta

*A few drugs developed by CDRI are manufactured and marketed by private companies.*

and inhibition of ovulation. The anti-implantation agents, like centchroman, mainly inhibit decidualization, alter implantation associated biochemical markers and suppress the local inflammatory reaction. In the male, the site and mechanism of action of antispermatic agents and heavy metals like cadmium have been studied. The functional maturation of epididymis has been shown to be an endocrine-mediated event, but some paracrine factors from testis are also involved.

**Studies on Intrauterine Devices (IUD):** Prolonged stay of (IUD) such a copper-T is devoid of noteworthy histological or biochemical changes in uterus or fallopian tubes. A reduction in uterine fluid leads to a many-fold increase in protein, urea and uric acid content. These, perhaps, make the milieu hostile to implanting blastocyst. IUD-induced bleeding is shown to be multifactorial.

**Anti-implantation Agents:** India is a global leader in the development and use of non-steroidal anti-implantation drugs. Ormeloxifene (Centchroman, CDRI) is a potent anti-estrogen and weak estrogen and hence a selective estrogen receptor modulator. It inhibits decidualization response to blastocyst, leading to implantation failure. After extensive clinical trials it is now marketed as a weekly oral pill in India (Saheli<sup>®</sup>, Hindustan Latex and Centron<sup>®</sup>, Torrent) and licensed abroad. Other indications

## INDIA AIDS WAR AGAINST AIDS

The fight against HIV AIDS plagued by exorbitantly high price of drugs marketed by MNC cartels.

CIPLA, a Mumbai based Indian company, produced Nevirapine made it available at 1/6th the prevailing global price. It is currently also producing Lamivudine, Stavudine and Zidovudine.

Other Indian companies joining the crusade to produce full range of anti-AIDS drugs and with substantial export include Orchid Chemicals & Pharmaceuticals, Aurbindo Pharma and Ranbaxy Laboratories.

include advanced breast cancer and dysfunctional uterine bleeding. Its ability to increase bone calcification could be beneficial in osteoporosis.

*The neem tree (Azadirachta indica). Besides azadirachtin, an antifeedant agent for controlling insects, the neem extract has spermicidal and hypoglycaemic properties*

*Immunocontraception:* Clinical studies with  $\beta$ -HCG tetanus toxoid vaccine developed at the National Institute of Immunology, despite variable protection, have indicated the feasibility of immunocontraception. Other potential leads include peptide sequence of GnRH, zona pellucida glycoprotein 3(ZP3) and riboflavin carrier protein (RCP) in the female and anti-FSH vaccine in the male.

*Spermicides:* The interest has increased due to the possibility of their having anti-HIV action also. CDRI is completing multi-centric Phase III study of *Sapindus mukorosi* based cream Consap. *Azadirachta indica* formulations are being developed by National Institute of Immunology (NII) and Defence Research Laboratories at Delhi.

*New Drugs and Devices:* Centchroman is being marketed as a weekly oral contraceptive and for advanced cases of breast cancer. *Plantago ovata* based cervical dilator (Isaptent, CDRI; Dilex-C<sup>®</sup>, Unichem) is useful in MTP and related procedures

*Animal Models:* WHO has accepted the CDRI

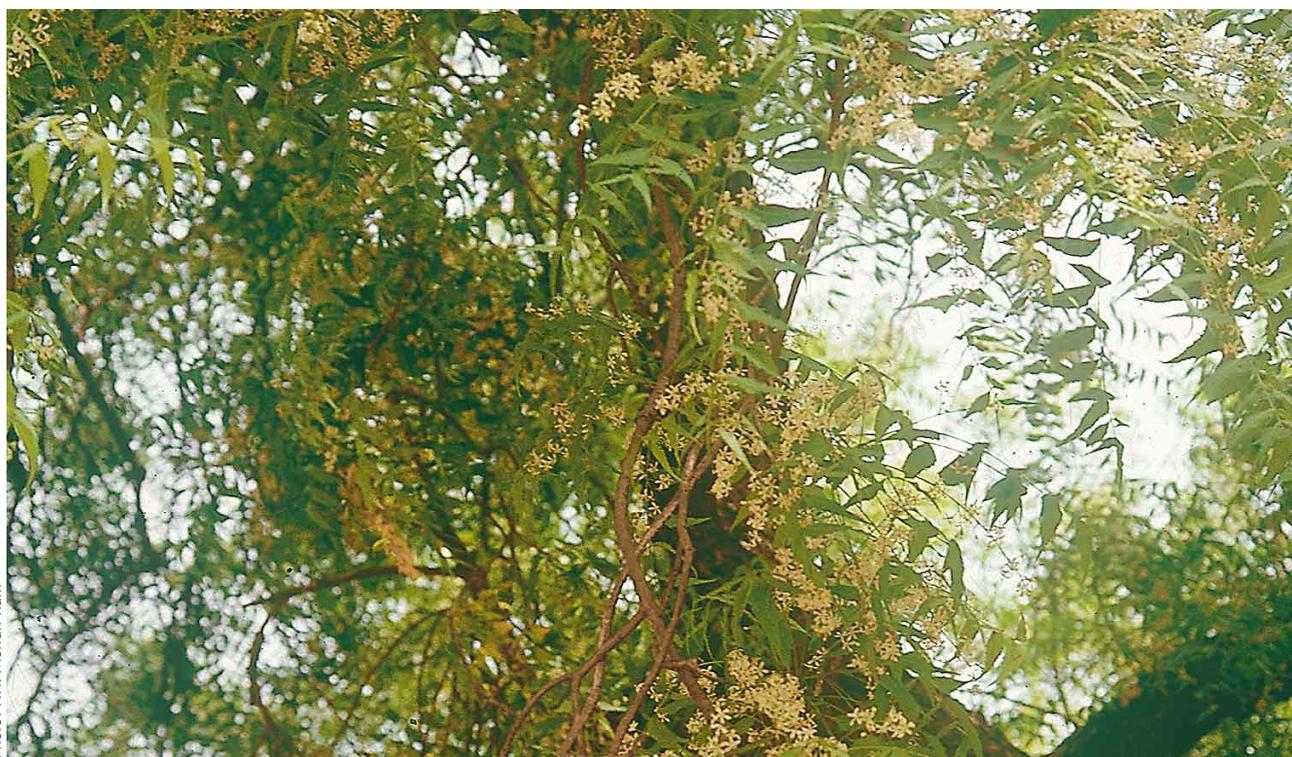


Photo: H.Y. Mohan Ram

bioassays for contraceptives as Mandatory Bioassays (MB). A monkey model of IUD bleeding has been developed.

## DIABETES

*Basic Studies:* Pancreatic  $\beta$ -cell has a common binding site for glucose and alloxan. Functions of insulin receptor in liver and RBC have been studied. Aspirin delays the onset and progression of diabetic cataract. Glucose has antagonistic effect on opioid receptor. Metenkephalin increases blood glucose level and the effect is reduced in streptozotocin diabetic rats.

*New Drugs:* A benzoquinazolone (Centpi-peralone, CDRI) was dropped due to side effects after Phase II clinical trial. Standardized *Pterocarpus marsupium* extract was effective in ICMR multi-centric trial. Some active constituents have been identified. Plants effective in streptozotocin model include neem (*Azadirachta indica*), bitter gourd (*Momordica charantia*), Chirayita (*Swertia chirayita*) and Jamun (*Syzigium cumini*). Several other plants have been reported active in the alloxan model.

## GASTROINTESTINAL TRACT

### HEPATOPROTECTIVE AGENTS

An *in-vivo* model for hepatic drug metabolism utilizes estradiol-induced vaginal cornification as the indicator. CDRI has standardized a comprehensive *in-vitro*, *ex-vivo* and *in-vivo* battery of tests to evaluate hepatoprotection. Eleven hepatotoxins (including ethyl alcohol and rifampicin) and 21 biochemical parameters are used. A major outcome has been development of Picroliv (CDRI), a standardized iridoid glycoside fraction of *Picrorhiza kurroa*. Phase III clinical studies are being initiated. Other plants shown to have significant activity include *Andrographis paniculata*, *Ricinus communis* and several species of *Phyllanthus*.

### PEPTIC ULCER

*Basic Studies:* Centrally mediated cytoprotection is afforded by dopamine (DA<sub>2</sub>), PGE<sub>2</sub>, GABA and endorphins, TRH and histamine

*A twig of varuna or barna (Crataeva nurvala). The bark is effective in dissolving stones in the urinary bladder.*

(H<sub>1</sub>) having an opposite effect. Peripheral protection is afforded by  $\beta$ -adrenergic blockers, estrogen and adenosine (A<sub>1</sub>) receptor agonist. Morphine has been reported both to inhibit and to aggravate and  $\mu$  and  $\kappa$  receptors have been implicated. Histamine and Ca<sup>++</sup> influx play a major role in ulcerogenesis.

*New Drugs:* Intensive study has been done on fruit pulp powder of edible banana (*Musa spp*). It affords protection by increasing mucosal resistance thus strengthening mucosal barrier. The DNA content of gastric juice is decreased. Protection has also been reported with several flavonoids, ursolic acid, nimbidin, tea and an Ayurvedic powder formation *Tamrabhasma*.

### OTHER STUDIES

Mastomys oesophagus and rat jejunum, have been used for assay of 5-HT (5-HT<sub>2</sub>) and acetylcholine respectively. Potent spasmolytic activity is reported in himachalol and related sesquiterpenes from *Cedrus deodara*, and coumarins clausmerin from *Clausena pentaphylla* and angelicin from *Heracleum thomsonii* respectively.

## CHEMOTHERAPY

*Diarrheal Diseases:* An experimental model of cholera has been developed in infant rabbit. The role of ORS in treating diarrhoeas has been established. A new serotype (*Vibrio cholerae* 0139) has been



Photo: H.Y. Mohan Ram



Photos: H.Y. Mohan Ram

**Top: *Commiphora wightii*, the source of guggul, an Ayurvedic medicine used by *Suśruta* for reducing body fat. The shrub has a green trunk with a fleshy bark. When incised, a yellow fluid oozes out. It dries up into a brown mass of oleo-resin gum;**  
**Middle: *Withania somnifera* (ashagandha), called the 'Indian ginseng' is used in hundreds of formulations in traditional Indian medicine;**  
**Bottom: *Bacopa monnieri*, a weed of wetlands, it is the source of *Memory Plus*<sup>®</sup> and *Nirvana*.**

characterized. New Indian vaccines for cholera and rotavirus are under clinical evaluation.

***Leishmaniasis:*** Indigenously developed liposomised amphotericin B is safer and shortens the duration of therapy. Similarly, 20 days combination therapy of aminosidine + sodium stibogluconate is as effective as over 40 days treatment with the latter alone. A primate model has been developed in *Presbytis entellus*. New IFA- and ELISA- based diagnostic tests have been developed (CDRI) and commercialized.

***Mycobacterial Infections:*** Clinical trials have been conducted to establish optimum Multiple Drug Therapy (MDT) regimens for leprosy and tuberculosis. Therapeutic utility of *Mycobacterium* (strains – ICRC, Cancer Research Centre; w, NII) vaccine in leprosy has been shown. CDRI non-pathogenic *Mycobacterium habana* based vaccine awaits evaluation.

***Mycotic Infections:*** *In-vivo* primate model has been developed to test anti-fungal drugs. An antifungal antibiotic Hamycin<sup>®</sup> (Hindustan Antibiotics Ltd.) one of the first one to be developed in India has been commercialized.

***Malaria:*** *Plasmodium knowlesi* model has been standardized in the rhesus monkey and has been used to demonstrate protective effect of  $\gamma$ -interferon. Artemesinin artether has been developed from *Artemisia annua*, a chinese traditional medicinal herb (CDRI and CIMAP) and marketed (*E-Mal*<sup>®</sup>, Themis) for resistant or virulent falciparum infection. A safer anti-relapse synthetic agent (*Bulaquin*, CDRI) has also been commercialized (*Aablaquin*<sup>®</sup>, Nicholas Piramal).

***Filaria:*** A primate model of human disease has been established in *Presbytis entellus*. Phase I-III WHO studies with Ivermectin and Phase III studies with low dose diethylcarbamazine (DEC) have been undertaken. Clinical studies have been done with DEC enriched salt and are in progress with the new macrofilaricidal amocarzine. Multicentric clinical (ICMR) and experimental evaluation of macrofilaricidal activity of the bark of *Streblus asper* is in progress.

## GLOBAL PRESENCE OF DR. REDDY'S LABORATORY

It is today India's most vertically integrated company with an annual turnover of US\$ 100 million (bulk drugs 36%, formulations 64%). It currently has marketing presence in 40 countries on all continents including USA and European countries.

Oral antidiabetic insulin sensitizers licensed to Novo Nordisk in 1998 are now in Phase II clinical trials.

The antidiabetic and dyslipidemic compound recently licensed to Novartis for US\$ 55 million.

## MEDICINAL PLANTS

The initial emphasis on validation of traditional claims has shifted to correlate activity with chemical constituents and GCP norm clinical studies with standardized preparations. Highlights not mentioned in the preceding sections are summarised below.

*Broad Based Screening:* CDRI has used over 100 *in-vitro* and *in-vivo* tests for broad-based screening of over 4000 plants and 600 marine organisms / 15% of the samples had significant activity providing leads for new drugs, pharmacophores or pharmacological tools. A high throughput screen has now been added. More limited programmes existed at RRL, Jammu, the CIBA and the Hoechst Research Centres, Mumbai.

*The ICMR Initiative:* ICMR is utilizing the 'Ward to Laboratory' approach in selected diseases with chosen products. The studies have demonstrated advantages of *Kshara-sootra* over surgery in anal fistula and anti-diabetic activity of the wood and bark of the leguminous tree bijasal or bijasara (*Pterocarpus marsupium*). Standardized preparations are ready for commercialization. Other studies are in progress.

*New Drugs:* Mention has already been made of Peruvoside, Gugulipid, Isaptent, Artether and *Bacopa monnieri*. RRL Jammu has commercialized

## Growth of Pharmaceutical Industry since 1950 in India

Parameter	Years		
	1950	1980	1990
Manufacturing Units	200	6400	23800
Investment	50m	6000m	21500m
Production	100m	14400m	170260m
Export	No Data	460m	53700m
Import	—	1130m	24580m

(The figures are number of manufactures and millions of Rs. for other parameters)

*Boswellia serrata* gum resin as NSAID (Sallaki®, Gufic). It is also hypolipidemic. The anti-parkinsonian *Mucuna pruriens* (Zandu) and immunomodulator from the plant guduchi (*Tinospora cordifolia*) (Seth GS Medical College, Mumbai) have also been marketed. The absence of a patent led to several pharmaceutical companies marketing products based on CDRI's work on psoralen for treating leucoderma.

*New Leads:* Coleonol (Forskolin) from *Coleus forskohli* is now a major experimental tool. Piperine as a "bio-availability enhancer" has great potential for use with drugs needing prolonged use or having low safety margin. Curcumin, from the turmeric plant besides being NSAID and anti-carcinogenic, has multifaceted actions. The clinical utility of *Ocimum sanctum*, *Withania somnifera*, *Tylophora indica* and *Terminalia arjuna* needs further evaluation. Several plants have facilitated adoption to high altitude (DIPAS, Delhi). The therapeutic utility of common food items like onion, garlic, ginger, fenugreek, and tea is receiving increasing attention. Interferon-like activity has been demonstrated in several plants.

## CLINICAL PHARMACOLOGY

Even though activity in clinical pharmacology was initiated at Seth GS Medical College, Mumbai in 1960, real spurt has occurred during the last two decades. Many colleges now have faculty positions, few have postgraduate programmes and some centres of excellence have

developed. The major areas of activity are summarized below:

**Clinical Trials:** The initial studies were Phase III studies with drugs already marketed abroad. These have continued. The development of new drugs in the country has generated expertise in Phase I and II studies as well. Several centres are involved in Phase II and III trials of standardized traditional drugs. Lately Phase IV (Post marketing surveillance) has been initiated for some drugs developed in India (e.g. Centchroman).

**Bioavailability:** Several centres undertake bio-equivalence studies but a few perform bio-availability of new drugs and formulations. New models are also being developed.

**Pharmacokinetics:** Studies have been done on a few drugs developed in India (e.g. Centchroman). The altered pharmacokinetics of known drugs in diseases like diabetes, hepatic, renal, cardiac and thyroid disorders, tuberculosis etc. has been extensively studied. The effects of age, genetics, time of administration have been studied. In addition, food-drug and drug-drug interactions (e.g. between oral contraceptives and antimalarials or antitubercular drugs) have received adequate attention.

**ADR Monitoring:** Multicentric programmes to monitor adverse drug reactions were initiated by the Drug Control Organization as well as ICMR. ICMR will soon initiate Phase II of the programme with a wider coverage and more focussed proforma.

**Other Studies:** These have included therapeutic drug monitoring (anti-convulsants and lithium), pharmacodynamic studies and survey of drug prescribing and utilization patterns to develop pharmaco-economics.

### OTHER STUDIES

**Venoms and Toxins:** Pharmacology of venoms of several species of scorpions

including *Buthes tamalus*, *Heterometrus bengalensis*, and *Isometrus thivaitesi* has been studied and responses shown to be mediated by phospholipase, 5-HT, histamine and prostaglandins present in the venom and by the release of autacoids like bradykinin. The toxic factor(s) in venoms of wasp *Vespi cinicta* (vecikinin), centipede *Scolopendra Subspinipes* (Toxin S), catfish *Heteropneustes fossilis* (HREF) and fish *Spherodites oblongus* etc. have been isolated and their actions analysed. Snake venom neutralizing activity has been observed in extracts of plants such as *Hemidesmus indicus* and *Pluchea indica*.

**Anti-inflammatory agents:** CDRI has developed the carragenin oedema test in mice as a screen for anti-inflammatory activity. IICT, Hyderabad has established new NSAID enfenamic acid and marketed it (Tromaril®, Unichem Laboratories, Mumbai). The work on curcumin (*Curcuma longa*) and boswellic acid

### New Drugs Developed in India

Year	Drug	Use	Organization
1956	Methaqualone	Hypnotic	CSIR
1958	Peruvoside	Cardiotonic	CSIR
1961	Hamycin	Anti-Fungal	HAL
1972	Cebltimizone	Anti-Thyroid	CSIR
1976	Sintamil	Anti-Depressant	CIBA-GEIGY
1980	Tromaril	Anti-Inflammatory	CSIR
1986	Cibemid	Anti-Protozoal	CIBA-GEIGY
1986	Gugulipid	Hypolipidaemic	CSIR
1987	Centbucridine	Anaesthetic	CSIR
1987	Centbutindole	Neuroleptic	CSIR
1991	Centchroman	Contraceptive	CSIR
1994	Chandonium Iodide	Neuromuscular Blocking agent	CSIR
1995	Centpropazine	Anti-Depressant	CSIR
1997	Thrombinase	Clot dissolving	JIPMER
1998	Artemisenin	Anti-malarial	CSIR
2000	Aablaquine	Anti-malarial	CSIR

## INDIA'S 'NUMERO UNO' EXPORTER OF DRUGS:

Ranbaxy Laboratories Ltd. New Delhi hit the headlines in 1970's by breaking the price stranglehold of a MNC on diazepam. Calmpose produced by it soon became a 'mega brand' (annual sale over Rs. 100 million).

Ranbaxy now produces about 50 bulk drugs with indigenously developed technologies. It markets them in India and 55 other countries with exports accounting for 45% of its total sales. It has factories in China, Netherlands, Ireland and USA.

Themis India is marketing Arteether (E.Mal) to over 40 countries. Artemether produced by Ipca Laboratories is exported to Sudan, Kenya and Hongkong.

(*Boswellia serrata*) has been mentioned earlier.

*Pulmonary Pharmacology:* The nature of 5-HT, histamine and acetylcholine receptors in various segments of bronchial tree in mastomys, rhesus and langur monkey has been analysed. ICMR is clinically evaluating several traditional remedies in bronchial asthma. Detailed studies have been done on anti-allergic activities of *Albizia lebbek*, *Picrorhiza kurroa*, *Solanum xanthocarpum* and *Tylophora indica*.

## PHARMACEUTICAL INDUSTRY

The Indian pharmaceutical industry, with a history of over 100 years, has progressed substantially during the last 50 years. The Industrial Policy Resolution of 1948 led to the setting up of Hindustan Antibiotics, Pimpri near Pune, Maharashtra in 1950s and IDPL plants in 1960s in the Public Sector and resulted in self-sufficiency in several major drugs. Another important milestone was the Patents and Designs Act of 1970, which allowed only process patents for pharmaceutical products. Both greatly accelerated the development of process technology and laid the foundation of the 'Pharma Revolution'.

**Process Technology:** The drug houses neither had the funds nor the resource base for indigenous technology after Independence. Hence technology was imported and modified if necessary. In some cases it was improved and even re-exported. Help was taken from national laboratories like NCL, Pune; IICT, Hyderabad and CDRI, Lucknow. In the next phase, in-house technology was developed and vertically integrated for important drugs like steroids, vitamins (A, B6), trimethoprim, diazepam etc. For some (e.g. Calmpose®) a strong brand equity was also built up. Gradually India became a leading global producer of drugs like ephedrine, d-propoxyphene, and clofazimine etc using indigenous technology. Several drug houses built their own R&D facilities and developed processes for new drugs like ranitidine, leading to dramatic reduction in national and even international prices. A recent example is CIPLA's success in making available the anti-HIV drugs at about one seventh of the international price. About 100 major drugs are produced using totally indigenous cost-effective technologies. Several processes for generic drugs have received international patents and bulk drugs, made in GMP norm factories, are exported to USA, Europe etc. There is increasing collaboration between the industry, academia and research institutions for vertically integrated and globally competitive technologies, especially for vital, expensive or patent-expiring drugs.

**New Drug Discovery Research (NDDR):** NDDR not only requires multidisciplinary facilities and expertise but also a large financial outlay. Few Indian companies were in a position to initiate such projects in early years. They collaborated with National Laboratories and the first drug was CDRI's anti-thyroid mipinazole (Centimizone®, Unichem) followed by IICT, Hyderabad's NSAID enfenamic acid (Tromaril®, Unichem). The multinational companies and Indian Companies such as CIBA and Hoechst, Sarabhai Chemicals and Public sector HAL and IDPL first set up

facilities for NDDR. Unfortunately these ultimately closed down. The two products marketed were Hamycin® (HAL) and Sintamil® (CIBA). The next 10 drugs were developed by CDRI and licenced to industry. During the last decade a few drug houses have developed NDDR facilities. The most active are Ranbaxy (Ranbaxy 2258, Parvosin) and Dr. Reddy's Laboratory. Several of their molecules are under clinical evaluation for benign prostatic hypertrophy (Ranbaxy 2258, Parvosin®), diabetes (DRF 2725, 2593) and cancer (DRF 1042). Cox-2 inhibitor, anti-asthmatic etc. are under advance pre-clinical assessment. Drug companies are also collaborating with academia and research institutions for synthetic or plant based drugs or for new dosage forms like liposomized amphotericin mentioned earlier.

### ECONOMIC INDICATORS

The pharmaceutical industry is self-reliant, vibrant and export oriented. Until 1960s the Indian drug prices were among the highest in the world and the country was a net importer. Today India is a net exporter and the Indian drug prices are

among the lowest. In some instances the difference is 30- (Flucanazol, Kenya) to 60- fold (Zantac, South Africa; Voltaren, Argentina). Several units can sustain NDDR. The data in Table give an indication of the tremendous growth of the pharmaceutical industry since 1950. The period has been divided in 2 or 3 segments. But growth in the last decades has been remarkable. The annual production of bulk drugs rose from Rs. 7,300 million to Rs. 31,480 million and of formulations from Rs 3,840 million to Rs. 13,920 million between 1990 and 1999.

The Indian companies have outperformed the multinationals (MNCs) operating in India from given below the percentage growth in select performance indicators such as total sales, gross profits and profit after tax in 2000-2001 over the preceding year.

The pharmaceutical Industry of India has developed the ability to respond quickly to new demands, has achieved a remarkably high degree of vertical integration, built units with world class GMP compliant manufacturing facilities, and has emerged as a globally competitive cost efficient producer of quality drugs and pharmaceuticals.

