

*twas*

Central Drug Research Institute

LUCKNOW, INDIA

CDRI



EXCELLENCE IN SCIENCE

*Profiles of Research Institutions  
in Developing Countries*

PUBLISHED WITH THE SUPPORT OF

the David  
Lusk  
Packard  
FOUNDATION

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Published by TWAS, the academy of sciences for the developing world,  
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# Foreword

Founded in 1983 and officially launched in 1985 in Trieste, Italy, by the secretary general of the United Nations, TWAS, the academy of sciences for the developing world, is dedicated to the promotion of scientific excellence and research capacity in developing countries.

With an initial membership of 42 'Founding Fellows', TWAS now counts 844 eminent scientists in 89 countries among its members. More than 85 percent of these scientists live and work in developing countries. This membership not only gives the Academy insight into the state of science in developing countries, but also provides a unique network of individuals and institutions through which the Academy can coordinate its activities.

Among these activities are the annual TWAS Prizes, designed to honour scientists in the South for their outstanding work in the fields of agriculture, biology, chemistry, earth sciences, engineering sciences, mathematics, medical sciences and physics. TWAS Prizes help bring the achievements of scientists working in the South to the attention of their national governments, providing them with a rare opportunity for recognition in their home countries. TWAS also offers research grants to individual scientists working in developing countries, as well as to research groups based in the world's least developed countries (LDCs). In addition, in collaboration with the governments of Brazil,

China, India and Pakistan, TWAS runs the world's largest South-South fellowship programme. Under this scheme, young scientists from one developing country are allowed to visit participating institutions in another developing country – particularly those mentioned above – to further their research, often by having access to equipment and materials not available at their home institution.

Institutions of scientific excellence in the developing world are included in a unique resource book, *Profiles of Institutions for Scientific Exchange and Training in the South*, produced jointly by TWAS, the Third World Network of Scientific Organizations (TWNSO), a TWAS-affiliated organization also based in Trieste, and the South Centre, based in Geneva, Switzerland. The third edition of this book, published in 2003, lists 525 such institutions located in 59 different countries in the South, and outlines their main scientific achievements, facilities and future plans.

Despite the perception that science in the South is lagging behind science being carried out in laboratories in the North, these 525 institutions provide evidence that top-quality research can be carried out in developing countries. And with a growing consensus that indigenous capacity in science and technology drives sustainable economic development, there is a need for more countries in the South to build their own scientific infrastructure – in terms of both human and institutional resources.

The purpose of this series of TWAS publications is to provide more details about individual 'centres of excellence', including how they developed, how their research pro-

grammes are organized, their achievements, their strengths and weaknesses, and – most important – how they can act as a model that other governments and organizations can follow when considering building scientific capacity. In this way, we hope the series will form a ‘blueprint for a centre of excellence’ that can be used by policy makers and those involved in the administration of national science policies.

The choice of which institutions to include in the series, which has been generously funded by the Packard Foundation, was difficult. However, it was felt that if the selected institutions all focused on a similar research area, then comparisons between institutions and countries would be simplified, making it easier to draw valid conclusions once several institutions have been studied. We have therefore taken advantage of the existence of a network of institutions created thanks to another TWNSO programme that focuses on the development of pharmaceutical products from medicinal plants. Despite the common theme, the institutions profiled in this series cover a wide range of activities, from the scientific validation of traditional medicines to the use of modern biotechnology. Taken together, however, these institutions are representative of a cross-section of countries in the South. They have also been instrumental in taking indigenous resources – in terms of local biodiversity – and transforming them into profitable commercial products available on local and international markets. In this way, these institutions are perfect examples of how capacity in science and technology can lead to innovation and socio-economic development.



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# Introduction and History



**C**hhitar Mal Gupta, director of the Central Drug Research Institute (CDRI), is not exaggerating when he says: “CDRI is one of the constituent laboratories of the world’s largest research organization.”

Indeed, CDRI is one of the 38 institutes and 80 field stations that make up India’s Council of Scientific and Industrial Research (CSIR) – an organization that employs some 20,000 staff, 15,000 of which are scientists and technicians.

Funded by India’s central government to the tune of 10 billion rupees a year (more than US\$200 million), CSIR accounts for the major part of the India’s science and technology spending. Each of the constituent 38 institutes is dedicated to a different area of research and development. There are those that focus on aerospace, for example, as well as botany, engineering, metallurgy and oceanography.

“A common theme for all these institutes” explains C.M. Gupta, “is that their research has to be industrially relevant.”

This is highlighted by the inclusion of the word ‘industrial’ in the organization’s name. In fact, it is estimated that, each year, nearly US\$1.3 billion worth of products are being manufactured using technologies developed by CSIR scientists.

CDRI, dedicated to the discovery and development of new drugs, is playing its part in the successful transfer of basic research into commercial products.

“We now have six successful commercial drugs,” says C.M. Gupta. “Two of these are purely synthetic, one is semi-synthetic and three are based on natural products.”

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## Then and now

CDRI recently celebrated its golden jubilee.

Established on 8 March 1949 in Chattar Manzil, an impressive palace built by the nawab rulers of the state of Uttar Pradesh in the 1700s, CDRI was officially inaugurated on 17 February 1951, shortly after India gained its independence. As such, it was one of the constituent institutes of the newly created CSIR.

“Since then, the institute has grown so that it now employs around 1,000 staff,” says C.M. Gupta, “including 200 regular scientists each with two or three graduate students, and some 400 technicians of various grades, from skilled laboratory workers to helpers.”

Today, through CSIR, the Indian government provides CDRI with an annual budget of some US\$6 million. In addition, it receives some US\$2 million each year from outside agencies, including royalties obtained through licensing arrangements from the sale of its six commercialized products.



“*The Indian government provides CDRI with an annual budget of some US\$6 million.*”

# Drug Development Pathway

“Our mandate has three main parts,” explains C.M. Gupta. “Judging from the name of the institute, the first two are probably obvious: to carry out basic research relevant to drug development and to develop new drugs, specifically for tropical diseases and population control measures. The third part of our mandate is to develop human resources. This is important because, when CDRI was created, there was no pharmaceutical industry in India. The government wanted CDRI to prepare the human resource as the first stage in building one.”

## THE CDRI CHARTER

- *Development of new drugs and diagnostics.*
- *Cellular and molecular studies to understand disease processes and reproductive physiology.*
- *Development of contraceptive agents and devices.*
- *Systematic evaluation of medicinal properties of natural products.*
- *Development of technology for drugs, intermediates and biologicals.*
- *Dissemination of information in the field of drug research, development and production.*
- *Consultancy and development of technical manpower.*



“ *Some 7,500 plants are recorded as having medicinal uses in India, but fewer than 20 percent are used in Ayurveda.* ”

Today, CDRI graduates are not only found at all levels in the continually expanding Indian pharmaceutical industry, but are also well represented among the staff of such multinational drug companies as Eli Lilly and Pfizer.

The development of human resources, plus the other two parts of the CDRI mandate, are put into practice via a unique series of inter-linking departments.

“CDRI is the only place in India where, under one roof, there is a department that conceptualizes a new drug molecule, supported by others that then screen it and put it through the required toxicological tests, pre-clinical and finally clinical trials,” says C.M. Gupta.

This diversity of departments could mean that the research carried out at CDRI might lack focus, with each department concentrating on its own particular research interests. However, the well-defined ‘chain’ of departments means that the whole process – from drug discovery and development to clinical trials and commercialization – is coordinated from beginning to end.

The process starts with the Division of Medicinal and Process Chemistry, which is responsible for discovering and designing new lead compounds with the potential to become commercial drugs. The division contains some 30 scientists, 100 research fellows working towards their PhDs and 50 technicians, bringing the total number of staff to 185 and making Medicinal and Process Chemistry CDRI's largest department.

“The progress of the institute is directly proportional to the output of this division,” claims Chandan Singh, the head of the division.

“We are the starting point of the whole programme,” continues Singh. “In this regard, we not only synthesize new compounds, but we also analyse natural products, including those found to be interesting through random screening and those listed in Ayurveda and other systems of traditional medicine.”

“One strength of the CDRI drug discovery programme is the traditional knowledge base that we have here in India,” confirms C.M. Gupta. “We try to use this throughout all research areas.”

### C.M. GUPTA, director



- In 1964, Chhitar Mal Gupta obtained his BSc from Rajasthan University, Jaipur, which was followed two years later by his MSc. He then moved to the Central Drug Research Institute (CDRI) to work on his PhD, which was awarded to him in 1969 by Agra University.

Between 1969 and 1973, Gupta worked first at CDRI and then at the Syntex Research Center, Palo Alto, California, USA. From 1975 to 1978, he was a research associate at the Massachusetts Institute of Technology (MIT), USA.

He then returned to India and, in particular, to CDRI, where he worked for 14 years, apart from a few months in 1981 when he spent some time again at MIT as a visiting scientist.

In 1992, he was appointed director of the Institute of Microbial Technology in Chandigarh, where he remained until his appointment as director of CDRI in 1997.

His research interests include the structure and dynamics of cell membranes and associated cytoskeleton organelles. By developing an understanding of these processes, he hopes to be able to target drugs to the specific parts of cells where their effects will be greatest.

Gupta is a fellow of the Indian National Science Academy (1989), the Indian Academy of Sciences (1987), the National Academy of Sciences, India (1991) and the National Academy of Medical Sciences, India (2000). In 2000, he was also elected as a member of TWAS, the academy of sciences for the developing world.

Even so, Singh stresses that the search for new drugs isn't confined to screening natural products. "Previously we were more vigorous in looking into natural products," he explains. "Now many of the scientists who did that work have retired and more focus is now being placed on synthetic chemistry because it can get us quicker results. There is also a middle road – the synthetic modification of natural products. In this case, if we find an interesting lead compound in a natural product, we can work entirely from chemical synthesis based on literature searches and other information, modifying the functional chemical groups to develop more effective compounds."

It is this expansion of traditional scientific thinking – in this case the 'improvement' of nature – that has led to the development of several of CDRI's successful products.



## CHANDAN SINGH, head of the Division of Medicinal and Process Chemistry

• Chandan Singh obtained his BSc and MSc degrees from Kurukshetra University in Haryana province in the north of India. He moved to Poona University near Mumbai for his PhD studies on the synthetic modification of triterpenes and the partial synthesis of alkaloids extracted from Buxus, an evergreen shrub. After graduating in 1976, he took a position as a senior research fellow at the All India Institute of Medical Sciences, New Delhi. In 1977, he moved to CDRI, where his work focuses on the isolation, characterization and synthetic modification of natural products, with a particular interest in antimalarial drugs. He has more than 60 publications and patents to his name and has played a leading role in handing over pharmaceutical production processes to industry.



As in any drug discovery programme, each individual compound or, in the case of natural products, standardized plant extract, must be screened for its biological activity. There are literally thousands of such screening tests to select from, but CDRI focuses on some 200, targeting its search for useful compounds on three main areas of research:

- Reproductive health, and devices and drugs for birth control, a major issue in the world's second most populous country. Basic research into reproductive hormones has also opened up other areas of biomedical research, including osteoporosis and breast cancer.
- Tropical and infectious diseases, especially tuberculosis and malaria, both of which are prevalent in India and many other developing countries. There are also research groups working on such parasitic diseases as filariasis and leishmaniasis that, like malaria, are transmitted by insect vectors.
- Ageing related diseases, including diabetes and hypertension. Such diseases, once regarded as problems only in developed countries, are now rising to epidemic levels in India, creating a need to develop in-house treatments.

Once a lead compound or interesting plant extract has been identified by scientists in the Division of Medicinal and Process Chemistry, it is passed on to other departments.

Among these is the Division of Pharmaceutics, headed by Satawayan Singh. Pharmaceutics is the science of drug preparations and dosage forms.

“The work of this division starts after the primary screening,” explains Satawayan Singh. “Its main aim is to standardize plant extracts and fractions and to determine the correct doses, form and route of administration to animals and humans.”

Among the main processes carried out by the Division of Pharmaceutics is the standardization of plant extracts. Plants contain a wide range of chemicals, each with concentrations that can vary during the plant’s life cycle. Some chemicals may be present at higher levels in young leaves, for example, or during flowering or fruit ripening. Some may also be harmful. Any attempts to develop pharmaceutical products from plant extracts, therefore, must rely not only on a detailed knowledge of what is present in the extract, but also of the relative concentrations of the different components.

To help with these analyses, many sophisticated instruments are available to scientists in the Division of Pharmaceutics, including a high performance thin-layer chromatography (HPTLC) machine. During the secondary screening process, different fractions of plant extracts are separated using HPTLC and the biological and toxicological activities of each fraction are evaluated. In many cases, unlike most modern drugs,



the activity of a herbal drug or plant extract may rely on a mixture of compounds. HPTLC allows the component compounds of different batches of extracts to be compared, giving not only their relative chemical properties (a guide to their identity that can be checked using standard control compounds), but also their relative concentrations.

“We can therefore standardize herbal extracts, with maximum and minimum limits for each component,” says Singh.

In fact, CDRI scientists were the first to develop and patent a ‘non-single compound’ drug – the hypolipidaemic or cholesterol-lowering Gugulipid, which contains about a dozen components. Prior to this, the isolation of pure molecules from plants and their further development to modern drugs constituted the basic objective of natural product research.

This changed when CDRI scientists developed Gugulipid as a standardized extract of the Ayurvedic remedy, gum guggulu, derived from *Commiphora mukul*. Laboratory tests, however, revealed that gum guggulu contained some toxic components, so an active fraction was isolated and standardized. It is now available as an ‘allovedic’ drug – Gugulipid – having completed all the necessary safety tests and clinical trials for it to be registered as a modern pharmaceutical.

This second example of ‘expanded scientific thinking’ marked a change in approach – or a new strategy – not only for CDRI, but also for other organizations involved in developing pharmaceutical products from natural sources.

“For such potential herbal drugs, we take about 10 batches of standardized extracts that can be used for all the different analyses that we have to carry out in the Division of Pharmaceutics and other places,” adds Singh. Following these tests, the standard specifications are agreed and fixed.

Other research carried out by staff in the Division of Pharmaceutics is aimed at developing the most effective delivery system for a candidate drug. In particular, the department has expertise in the development of oral controlled release pharmaceuticals and nasal and transdermal drug delivery systems.

“We are aiming to develop a pill, to be taken once every 12 to 14 hours, that will slowly release the active compound, rather than a pill that must be taken every 3 to 4 hours,”

“

*According to the Food and Drug Administration (FDA) in the USA, 75 percent of drugs entering phase I trials make it to phase II; 42 percent of drugs entering phase II trials make it to phase III; and 64 percent of drugs entering phase III trials get approval. Overall, only 23 percent of drugs that enter phase I trials are eventually approved.*

”

## SATAWAYAN SINGH, head of the Division of Pharmaceutics



• Satawayan Singh received both his bachelor's and master's degrees in pharmaceuticals from the renowned Banaras Hindu University at Varanasi, some 250 kilometres southeast of Lucknow. He joined CDRI's Division of Pharmaceutics in 1969 and obtained his PhD in pharmaceuticals shortly afterward. With interests in quality control and delivery systems for new drugs, he now has some 70 scientific publications and 80 patents to his name. In 1992, he was made head of the Division of Pharmaceutics. Today his research interests lie in the latest physico-chemical techniques used in the development of quality control and modern drug delivery systems, including microparticles and transdermal dosage forms. He is a lifetime member of the Indian Pharmaceutical Association and serves on the expert panel for the inclusion of plant-based and herbal drugs into the Indian Pharmacopoeia.

explains Singh. "Such a formulation will depend on the physical parameters of the active pharmaceutical ingredient, or API, including the physico-chemical properties of the formulation – the type of polymer and other so-called 'excipients' used as binders and diluents in the formulation."

Each lead compound identified by CDRI scientists must also pass a battery of toxicological tests.

"The Division of Toxicology at CDRI is the only place in India which offers complete facilities under one roof," says Sudhir Srivastava, head of the division. "We have the capability to carry out the full range of toxicity studies to conform to the requirements of international regulatory authorities for the development of new drugs and vaccines."

The division is composed of seven scientists, six technical officers, eight technical support staff and six laboratory attendants and animal handlers. Among the scientists are experts in systemic toxicology, with a focus on histopathology (including Srivastava himself), clinical biochemistry, haematology, hypersensitivity, and reproductive and developmental toxicity.

"In the past 40 years, we have carried out toxicity studies on more than 60 candidate drugs and vaccines. The protocols we now follow are based on guidelines issued by the

Organization for Economic Cooperation and Development (OECD). However, our approach is flexible and comprehensive – it adapts to changes quickly and complies with the requirements of other important regulatory bodies as well,” explains Srivastava. Details



of the different toxicological studies carried out by the divisions’s scientists are outlined in Table 1. Most of the tests are routinely performed on animals such as mice, rats and rabbits, although *in vitro* assays using cultured cells are also used.

“The subject is always evolving with newer and better methods,” says Srivastava. “Nowadays we are using fewer animals and moving more and more towards cell-based systems.”

Table 1: Toxicity studies being carried out at CDRI.

Toxicity test	Sub-class of toxicity test
Local toxicity	<ul style="list-style-type: none"> <li>• skin irritancy</li> <li>• mucous membrane irritancy</li> </ul>
Systemic toxicity	Rodent and non-rodent. The duration of the tests depends on the intended duration of human exposure.
Reproductive and developmental toxicity	<ul style="list-style-type: none"> <li>• fertility and reproductive performance</li> <li>• teratogenicity (the ability to cause defects in a developing foetus) studies</li> <li>• peri- and post-natal studies</li> </ul>
Genotoxicity and mutagenicity studies	<ul style="list-style-type: none"> <li>• <i>in vitro</i> tests for chromosomal aberrations and the ability to cause cancer in human lymphocytes</li> <li>• <i>in vivo</i> test for chromosomal aberrations in mouse bone marrow</li> </ul>
Carcinogenicity studies	<ul style="list-style-type: none"> <li>• short- and medium-term bioassays</li> <li>• life-long studies (mouse, 18 months, and rat, 24 months)</li> </ul>
Allergy and hypersensitivity testing	<ul style="list-style-type: none"> <li>• mouse ear swelling test</li> <li>• local lymph node test</li> <li>• guinea pig maximization test</li> </ul>

## SUDHIR SRIVASTAVA, head of the Division of Toxicology



- *Sudhir Srivastava has both Bachelor of Medicine / Bachelor of Surgery (MBBS) and Doctor of Medicine (MD) degrees and now specializes in systemic toxicology. He first came to CDRI in 1986 and, in 1990-91, spent 16 months in Germany on a German Academic Exchange Service (DAAD) fellowship to study in vitro toxicology. Promoted to CDRI area coordinator in 1994, he has been head of the Division of Toxicology since 1999 and now oversees a staff of 26. Among his other interests is the promotion of Good Laboratory Practice (GLP) compliance in toxicological research. As part of this work, along with colleagues at the World Health Organization (WHO) he has produced a book, Non-clinical safety testing. He is also a certified WHO/GLP trainer and an inspector with a GLP monitoring authority based in New Delhi..*

Standard operating procedures (SOPs) have been developed for all these tests and are adhered to rigorously to ensure good laboratory practice (GLP) compliance – an issue close to Srivastava’s heart (see ‘Key personnel’ box this page). “These procedures cover instructions from the simplest to the most intricate of scientific techniques as well as administrative procedures,” he explains. “Written protocols of all studies are strictly followed during the course of a study and any deviation from these protocols is recorded in detailed amendments in the study report.”

Toxicity study reports include such information as the objective of the study, full details of the composition and stability of the substance being tested (the division possesses facilities for such analyses), a description of the tests performed, and detailed descriptions of the results, the statistical procedures used to analyse them and other relevant information.

“Once completed, these reports are signed by the study director and other senior staff and consultants,” adds Srivastava.

Once the toxicological properties of a lead compound or standardized herbal extract have been worked out, the potential drug product is passed to the Division of Pharmacology where its safety profile is further examined.

“First we carry out six or seven main tests,” explains Ram Raghubir, head of the division. “Then we decide which other tests need to be done. In all, we have 85 different screening tests available in the department.”

Previously, these tests centred mainly on animal experiments but, as with other organizations involved in drug development, there has been a move towards more cell and molecular target-based tests. In addition, the CDRI drug-testing regimen initially followed the Indian government’s regulatory system, which included a mandatory three-day check for acute toxicity. Now, however, with the international market in mind, CDRI’s protocols have been tightened to comply with the requirements of the European Union countries and the United States and, in particular, to tie in with the regulations of the Organization for Economic Cooperation and Development (OECD) and the Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA) in the USA through the International Conference on Harmonization (ICH) guidelines. Under these more stringent regulations, for example, a 14-day check for acute toxicity is required.

In addition to the acute toxicity tests, staff in the Division of Pharmacology carry out seven other types of basic tests. These include behavioural activity studies; studies on the central nervous system; checking haemodynamic characteristics such as heart rate and blood pressure; examining gastrointestinal function, including gut motility and gastric

### **RAM RAGHUBIR, head of the Division of Pharmacology**

- *Ram Raghubir joined CDRI in 1974 with a degree in veterinary science and worked as a scientist in different areas. He eventually registered for a PhD and graduated in 1980. Since then, his research has focused on electrophysiology, pain and analgesia, particularly with regard to the basic cellular and molecular mechanisms involved and how these can be used to aid rational drug design and development. He was also instrumental in developing CDRI’s programme in the search for compounds that help in wound healing. He became head of the Division of Pharmacology in 2001, where his current interests lie in understanding the molecular mechanisms that lead to cerebral stroke (ischaemia) and developing new anti-stroke treatments. He also supervises the institute’s regulatory pharmacology programme.*





irritation that could lead to the formation of stomach ulcers; urine tests for metabolites; interactions with other drugs; and isolated tissue studies, for example on the ileum and uterus.

As in other departments, as well as working on the institute's drug development 'chain', the eight scientists in the Division of Pharmacology also carry out their own research. Their major research and development focus are the discovery and development of new lead compounds and new products for diseases of the cardiovascular and nervous systems, as well as age-related disorders.

Ram Raghbir, for example, is now studying the molecular mechanisms that lead to cerebral stroke, or ischaemia. Naturally, the long-term aim of such basic research ties in with the institute's drug development programme. In this case, Raghbir is also testing the effects of a new herbal preparation in preventing and reversing the damage caused by reduced blood supply to the brain. Experiments performed in rats suggest that the extract could be both preventative and curative – making it a potential 'blockbuster' drug.

The final experimental 'links' in the drug development chain are the clinical trials. At CDRI, these are conducted by the Division of Clinical and Experimental Medicine, which hosts four scientists, all of who are doctors of medicine. The division is headed by Omkar Asthana.

Again, the trials follow International Conference on Harmonization (ICH) guidelines, which means that patients must give their prior informed consent before taking part in the studies.

Clinical trials are divided into three stages.

"In phase I trials, clinical studies are performed on healthy volunteers to check for drug safety and tolerability," says Asthana. "In phase II, we carry out controlled, limited



“According to the Food and Drug Administration (FDA) in the USA, the time between a drug entering its first human trials to when it obtains approval averages 5 to 6 years, but the process can take up to 12 or even 17 years.”

trials to check the efficacy of the drug on patients suffering from the target ailment,” he continues. “Phase III trials, on the other hand, are large, multi-centric studies and can involve hundreds of such patients.” Phases II and III also involve the use of a control standard drug that is used to compare the efficacy of the new drug.

The development of an antimalarial drug,  $\alpha/\beta$  arteether, now being marketed successfully in India and Africa, involved 28 healthy volunteers for the phase I trial, 49 malaria-infected patients in the phase II trial, and 478 patients at several centres throughout India where the disease is endemic in the phase III trial.

Such procedures not only require adequate planning – usually in collaboration with other research institutes and hospitals – but are also expensive. Costs can also rise depending on the drug being tested. In the case of an antimalarial compound, for example, the course of treatment is for three days only, by which time the parasites are removed from the blood. “With drugs to treat hyperlipidaemia and diabetes, however, due to the nature of the diseases, the drugs must not only be less toxic, but treatments can go on for months or even years. Thus there are quality-of-life issues to take into account,” explains Asthana. “The duration of our clinical trials has to reflect this.”

Over the years, the number of drugs entering the CDRI clinical trial programme has varied.

“In the 1970s we performed 10 to 12 phase I trials, but only half of this number during the 1980s. Part of the reason for this was that five or six of the compounds we tested in the phase I trials were taken forward into phase II trials. In the 1990s, phase III trials came on line,” explains Asthana.

In all, up to 1998, 12 drugs successfully completed phase III clinical trials and were licensed for use in India. Since then, however, as emphasized by the work being carried

out by other divisions at CDRI, clinical trials are now designed in accordance with more strict international regulatory guidelines.

“As India is opening up, we need to look for licensing outside the country. Therefore we need to follow international standards,” adds Asthana.

There has also been a shift in the selection criteria for drugs that will be put through clinical trials, with decisions increasingly based on commercial viability and risk-benefit analyses.

“Since the 1990s we have been looking for novelty among the products we develop,” says Asthana. “We must be able to show that we hold the intellectual property rights to the drug. We have, for example, dropped a promising anthelmintic drug from phase II trials because all the information on it had already been published. In such a case, we could not find any commercial company willing to take on the risk of producing it.”

“The policy has changed,” confirms Chandan Singh, head of Medicinal and Process Chemistry. “Earlier, we developed compounds to the point of clinical trials, but now we do not develop a lead compound unless the industry is interested. It would be considered money wasted. Previously, the government was more liberal and wanted us to do every-

### **OMKAR P. ASTHANA, head of the Division of Clinical and Experimental Medicine and coordinator of clinical trials**



- *Omkar P. Asthana joined CDRI in 1976 as a clinical pharmacologist and, by 1993, had worked his way up to become head of the division where his main task is to coordinate the institute's clinical trial programme. He obtained his MD and DCH from King George Medical University, Lucknow, and received two years' further training at the J.W. Goethe University Medical Clinic, Frankfurt, Germany. During this time, he worked in close collaboration with the product development departments of such Germany-based multinational pharmaceutical companies as Hoechst AG and Knoll. He is a fellow of the national Academy of Sciences, India, and has received fellowships from the World Health Organization (WHO), the German Academic Exchange Service (DAAD) and the Indian Council of medical research (ICMR). In connection with his clinical research activities, he has also travelled to Hong Kong, Japan, Malaysia, Thailand and the United States.*

thing. Now, however, as with many governments in the developed world, the Indian government is of the opinion that industry should fund near-market research.”

“For this reason, we focus on lead compounds that are better – in the sense of being more effective, safer and cheaper – than the currently available drugs, even if we hold the rights,” adds Asthana. A lead synthetic molecule developed by CDRI scientists in the 1970s that had useful anti-filariasis properties, for example, was dropped during phase II clinical trials when it was shown to be no better than the current market leader.

This focus on international markets, the filing of patents in the United States and European Union, and the identification of partner companies willing to help develop new lead compounds is the work of a separate fully-fledged division in the CDRI drug development chain, the Technical Information, Industrial Liaison and Planning Division, headed by Zaka Imam.

“This division has four main responsibilities,” he says. “First is planning, monitoring and evaluating the institute’s research programmes. This is based on a five-year plan that



we submit to our headquarters in New Delhi for approval. Then, each year, we must prepare an annual report and a workplan that includes budget details for the following year.

“The second area this division focuses on is business development,” continues Imam. “This is something we now build into every research programme. Whether it is aimed at the development of new lead compounds or new processes, we try to link each project with a business development objective, a sponsored or collaborative project, or a commercial product. We also offer training courses that have been attended by developing-world scientists on World Health Organization (WHO) fellowships.

## ZAKA IMAM, head of the Division of Technical Information, Industrial Liaison and Planning Division



- *Zaka Imam is a science and technology manager with more than 25 years experience. After obtaining his PhD in zoology from Aligarh Muslim University, Aligarh, he spent more than three years as an assistant editor with Science Reporter, India's leading science magazine, and an additional year in charge of production of the Indian Journal of Medical Research. He has also published more than 150 popular science and news articles in national newspaper and magazines, as well as contributing some 16 news stories to such renowned publications as the British Medical Journal, The Lancet and Nature. He joined CDRI in 1980 to serve as editor of the institute's current awareness publications on drug research and development. In 1986 he transferred to the Division of Technical Information, Industrial Liaison and Planning, becoming head of the division in 1992. He has experience in planning, programme appraisal, information management, international collaboration, intellectual property rights and technology licensing. In addition, he is a member of the editorial board of the International Journal of Health Technology and Management, and the Indian Science Writers Association, Lucknow.*

“Linked to our research and development, we have a policy to protect our intellectual property. This is an area in which we are becoming increasingly active. In January 2005, for example, the new World Trade Organization (WTO) product patent regime came into force, affecting those Indian pharmaceutical companies that make generic drugs. To protect our intellectual property, therefore, we have started filing patents in European Union, Japan, the United States and elsewhere. Our strategy is targeted, however. For example, our antimalarial drugs will only be protected by patents primarily in those countries where malaria is endemic. This helps us keep down the costs of filing international patents.

“Finally, this division is also responsible for organizing international collaborations,” adds Imam. “These are often coordinated through the Indian government or as part of CDRI or CSIR programmes. The division also coordinates training of institute staff in various disciplines, including management.”

Thus, the Technical Information, Industrial Liaison and Planning Division plays an integral part in the institute's drug development chain. Indeed, the most important 'link' in the chain – that responsible for the commercial development of the scientists' endeavours – may be the link between the publicly funded research institute and private companies. Without such a link, the fundamental research being carried out in the institute's laboratories would be unlikely to develop into commercial products. As it is, CDRI – by any measure – is a thriving institute that has not only developed and produced effective pharmaceuticals but, in doing so, has helped Indian companies overcome technological challenges and, therefore, has contributed to the country's economic development.



“*Despite having a population of more than billion people, India has a largely untapped pharmaceutical market. Per capita expenditure on health care in India is US\$93, compared to US\$453 in Brazil and US\$189 in Malaysia, two other developing countries with large populations.*”

# Measures of Success

CDRI's director, C.M. Gupta, makes a proud boast.

“Whatever the assessment is based on, CDRI is one of CSIR's premier institutions.”

Not only that, but he also claims that: “Since 1997, we have taken a crash-course in modernization and upgraded our expertise. Now we are one of the best institutions of our kind in the developing world and, given our size, we are competing quite well with the developed countries.”

Measures of scientific success can be difficult to quantify, but there are certain research and development ‘outputs’ that can be assessed.

Among these is the number of scientific papers published by researchers at the institute. Figure 1 shows that there has been a general increase in this output since the creation of CDRI in the early 1950s, peaking at an average of nearly 250 papers a year during the 1980s. Even more impressive is that some 60 to 70 percent of these papers have been published in international journals.

Although there was a slight decrease in the number of publications during 1991-2000, this was off-set by the increase in the papers’ ‘impact factor’ – a measure of the importance of the journal in which a paper is published based on how many times other scientists refer to papers in the journal.



“In 1998, our average impact factor was 1.4,” says C.M. Gupta. “By 2004, this had increased to 2.1, which is a substantial improvement. Not only that, but the number of papers we are publishing in journals with an impact factor of greater than 2.0 increased from around 20 in 1998 to 68 in 2003.”

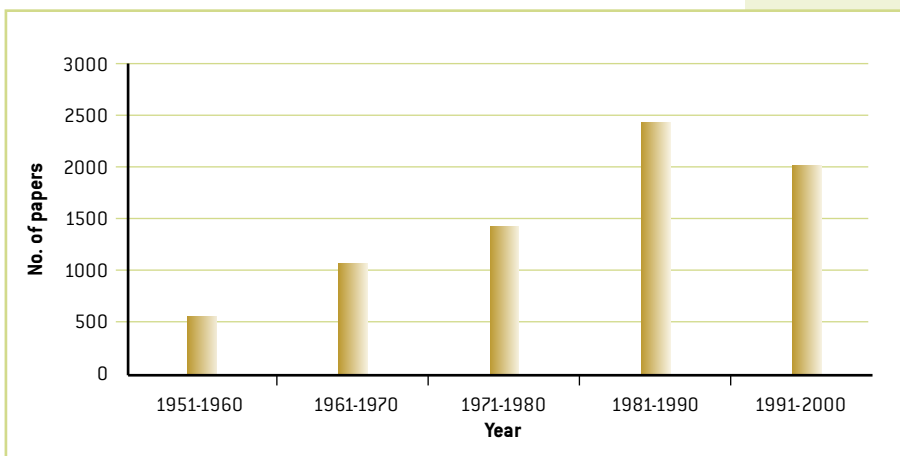
Between 1951 and 2000, CDRI scientists also contributed almost 350 chapters to books produced by such renowned publishers as Academic Press (New York, USA), Elsevier (Amsterdam, the Netherlands) and Verlag (Basle, Switzerland), as well as Indian publishers. Some 150 of these chapters, or more than 40 percent, were published between 1991-2000.

In addition, researchers at CDRI published 45 books between 1951 and 2000, all but five of which were produced between 1981 and 2000.

Another measure of scientific output is the number of students that receive advanced training.

As highlighted earlier by CDRI director, C.M. Gupta, such human resource development is a major priority of the institute and between 1951 and 2000, some 750 students graduated with PhD or DSc degrees after having spent some time at CDRI, and other 150 with MSc or doctors of medicine degrees. The institute itself, however, is not registered as a degree awarding body, and therefore these degrees were awarded in collaboration with Agra University, Kanpur University, Lucknow University and others.

Fig 1: Scientific publications by CRDI researchers, 1951-2000.





## EQUIPMENT

• CDRI's research programmes are equipped to meet the challenges required to develop modern pharmaceuticals using. New facilities include a state-of-the-art robotic multiple organic synthesizer that is able to construction libraries of closely-related chemical compounds. In addition, the institute has invested in a robotic high-throughput screening facility – the first of its kind in India – and a structural biology facility for predicting molecular structures – particularly useful for targeted drug design. In addition, a confocal microscope assists investigations into the mechanisms of drug action and an electron microscope helps to better understand drug action at the cellular level. DNA microarray and proteomics facilities have also been installed, together with computer software for bioinformatics and computational biology, all of which allow CDRI to compete at the forefront of drug development science.

## FACILITIES

More recently, CDRI has entered into a partnership with Jawaharlal Nehru University in New Delhi under which the institute also offers students coursework and the opportunity to carry out research projects.

“There are now more than 220 students here, 60 percent of which are on CSIR fellowships, a form of funding much sought after by Indian graduates,” says C.M. Gupta. “This pool of young minds is actually one of CDRI's greatest strengths. They work hard, and are the real performers in the institute. Not only that, but they bring in fresh blood and new ideas to the research programmes – they are the work horses of the institute.” So, just as the students benefit from the teaching and research infrastructure set up at CDRI, so does the institute benefit from the dynamism of the students – a true symbiotic relationship.

That this relationship is of benefit to the students is confirmed by Chandan Singh: “Once they have graduated, our students very quickly find employment. The Indian



“*India accounts for more than 15 percent of the world population but just one percent of the global pharmaceutical industry.*”

pharmaceutical industry, for example, is mostly managed by people trained at CDRI some 20 to 30 years ago. Some students do go abroad to gain post-doctoral experience, but now many come back and most of them work in industry.”

This throughput of young scientific talent and output of scientific publications is all aimed at satisfying the institute's mandate, which includes the development of new drugs and technical processes.

An idea of the institute's success in these areas can be gained from analysing the patents that it has applied for and been granted, both in India and abroad (Table 2).

*Table 2: Number of patents filed by CDRI (1951-2000) in India and internationally.*

<b>Years</b>	<b>Indian patents filed</b>	<b>International patents filed</b>
1951-1960	16	0
1961-1970	26	2
1971-1980	90	21
1981-1990	118	11
1991-2000	175	69
<b>TOTAL</b>	<b>425</b>	<b>103</b>

As with the number of scientific papers published, there is a large increase in the number of patents filed in the past 20 years compared to the 20-year period between 1961 and 1980. There has also been a shift in emphasis from filing Indian patents, which made up more than 90 per cent of the total number filed between 1981 and 1990, to filing international patents, which made up nearly 30 percent of the total number filed between 1991 and 2000. Also during the last two ten-year periods, the number of international patents filed increased from 11 to 69.

The result of all these patents – perhaps more visible to the public – is a series of products licensed to private companies and available on the market in India and elsewhere. These commercial products provide the fourth measure CDRI's success. Indeed, 12 out of the 17 new drugs discovered and developed in India have been discovered and developed at CDRI (Table 3).

Three of these products can be used to highlight the different approaches that CDRI has taken in developing drugs and herbal remedies, namely a standardized extract developed as a herbal remedy, a standardized extract developed as a modern medicine, a semi-synthetic product marketed as a pure product and a purely synthetic product.



Table 3: New drugs discovered and developed in India.

Product	Year	Use	Institution
Urea stibamine	1921	Anti-kala-azar (Leishmania)	Trop. Med., Calcutta
Hamycin	1961	Antifungal	Hal, Pune
Forskolin / Coleonol	1970	Pharmacological tool and new lead structure	Hoechst & CDRI
Centimizone	1972	Antithyroid	CDRI
Sintamil	1976	Antidepressant	Ciba-Geigy, Mumbai
Tinazolin	1978	Nasal decongestant	Ciba-Geigy, Mumbai
Tromaril	1980	Anti-inflammatory	CSIR RRL*, Hyderabad
Gugulipid	1986	Hypolipidaemic	CDRI
Centbucridine	1987	Local anaesthetic	CDRI
Centbutindole	1987	Neuroleptic	CDRI
Centchroman	1991	Contraceptive	CDRI
Chandonium iodide	1994	Neuromuscular blocker	CDRI
ProMind	1996	Memory and learning enhancer	CDRI
Centpropazine	1997	Antidepressant	CDRI
Arteether	1997	Antimalarial	CDRI & CIMAP*, Lucknow
Elubaquine	2000	Antimalarial	CDRI
Consap	2004	Spermicidal	CDRI

CDRI scientists are responsible for discovering and developing 12 out of 17 new Indian drugs

\* RRL = Regional Research Laboratory, CIMAP = Central Institute of Medicinal and Aromatic Plants.

## ANIMAL HOUSE

- In all, the CDRI animal house breeds and distributes 26 species and strains of animal, including mice, rats, guinea pigs, rabbits dogs and mastomys – a rat-like rodent.

Indeed, the facility is one of India's two national facilities for laboratory animals. The other is located in Hyderabad in the central area of the country. The mandate of these two facilities, as designated by the government of India's Department of Biotechnology, is to produce and distribute animals that are certified both genetically and microbiologically. In addition, the CDRI facility is recognized by the government's Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), a representative of which sits on the Institutional Animal Ethics Committee, along with vets, pharmacologists, zoologist and legal experts, that must approve all animal experiments. The guidelines used by this committee, as with other guidelines followed by CDRI (see pages 9 and 11) are based on the best international standards set by the WHO, the European union and the United States' Institute of Health. The truth of the matter is that, despite an increasing number of pharmacological tests that can be carried out on cell lines – and the CDRI animal house also maintains such cultures – animals are still required for the majority of drug development assays and analyses. Indeed, certain species and strains are used specifically for certain diseases – gerbils provide a good model for filariasis, for example, monkeys for malaria and the DBD strain of mouse for diabetes.

CDRI also operates a 'rehabilitation programme' for the primates that it uses in its experimental procedures. Once an experiment is completed, the monkeys are released into a large cage on the CDRI campus where they are able to interact socially and, indeed, where they breed freely.



## FACILITIES

## Memory enhancer: *Bacopa monniera* standardized extract

Two standard Ayurvedic treatises, 'Charak Samhita' and 'Sushruta Samhita', describe brahmi, derived from *Bacopa monniera* or water hyssop as being able to enhance memory and cure mental retardation. Indeed, brahmi has been used for some 3,000 years as a brain tonic.

Due to its reputation as a memory augmenting plant, *B. monniera* has attracted the attention of Indian chemists for several decades. The first chemical examination of the plant was published by CDRI scientists in 1960. Further systematic analyses were also published in the 1960s. CDRI scientists isolated and characterized two triterpenoid glycosides from the plant that were designated bacosides A and B.

Neuropharmacological investigations of *B. monniera* extracts have since confirmed the traditional claims. Following ethanol extraction and butanol fractionation, a standardized preparation derived from the plant has been shown to contain not less than 60 per cent bacosides A and B in the total mixture of bacosides. This standardized extract was tested in rats using two standard laboratory techniques to assess learning – namely the brightness discrimination reaction response and the active conditioned avoidance response. In both sets of experiments, the standardized brahmi extract showed a significant facilitatory effect in treated animals compared with untreated controls. In addition, regulatory pharmacological studies showed that the extract did not produce any untoward effect on gross behaviour and innate and motivated responses, even at doses 25 times higher than the effective dose.

“*The Indian pharmaceutical industry consists of some 300 large manufacturing units and 18,000 smaller producers, a situation that creates a competitive market and helps keep prices – and returns – low.*”

In subsequent investigations, the efficacy of the memory enhancing effect of bacosides on experimental models of amnesia – using immobilization and scopolamine induced stress – in trained rats was tested. Pretreatment with bacoside attenuated these amnesias. Furthermore, at the recommended therapeutic dose level, no systemic pharmacological or toxicological effects were found to be induced by the bacosides. They were also found to be safe in sub-acute toxicity studies in both rodents and primates.

Preclinical neuropharmacological studies demonstrated that both brahmi extract and bacosides improved short-term and intermediate memory, thus improving long-term memory.

Based on these wide-ranging studies, the Drugs Controller of India granted CDRI permission to conduct phase I clinical trials on healthy human volunteers. These trials did not reveal any undesirable effects. However, due to the time and costs that would have



been required to conduct further clinical studies, it was decided to market the standardized fraction of the plant extract as a herbal drug.

This standardized preparation was licensed to a private company. Its commercialization was formally launched by the then prime minister, Narsimha Rao, in February 1996. The product was marketed and exported to several countries.

In 2001, the product was licensed to Lumen Marketing, Chennai, India, which commercialized the product under the name ProMind in 2002.

Meanwhile, limited clinical trials of the herbal product have been carried out in elderly persons with age associated memory impairment and children affected by attention deficit hyperactivity disorder, and the preparation has been found to improve their condition without any adverse effects.

## An ‘allovedic’ drug for lowering blood cholesterol: Gugulipid

The lead for the development of Gugulipid as a hypolipidaemic drug again came from the tradition of Ayurvedic medicine, which prescribes gum guggulu – derived from the plant *Commiphora mukul* or false myrrh – for the treatment of certain cardiovascular disorders, gout and arthritis.

The product owes its origin to the basic work on crude gum guggulu carried out at Hindu Banaras University in the 1960s. In 1970, samples of guggulu were sent to CDRI for the evaluation of their hypolipidaemic activities. Primary biological screening carried out at CDRI indicated the potential lipid lowering capabilities of the gum and the results were first published in 1971.

Samples were also sent to the National Chemical Laboratory, Pune, where various fractions or oleoresin of gum guggulu were analysed and the individual chemical components successfully identified. Meanwhile, scientists at CDRI evaluated the biological efficacy and toxicity profile of different fractions of gum guggulu. They identified a toxic and inactive portion that was insoluble in ethyl acetate, and a safe and active portion that was soluble in ethylacetate and contained compounds identified as guggulsterones. This ethyl acetate soluble fraction was named as gugulipid, the active ingredients of which are mainly guggulsterones E and Z, and patented.

Clinical trials conducted by CDRI scientists showed that gugulipid reduced serum cholesterol and triglycerides by an average 24 per cent and 22 per cent respectively, and that some 260 of a group of 330 hyperlipidaemic patients responded to treatment. The results clearly indicated the efficacy of gugulipid and that it was tolerated better than clofibrate, the alternative available drug. Based on these results, in 1986, the Drugs Controller (India) gave permission to market gugulipid as a new drug.

An agreement for commercialization was signed with Cipla Ltd., Bombay, in January 1987, and the technology was formally released to the company by the former prime minister Rajiv Gandhi.

Commercial production of gugulipid began in October 1987 and it was marketed – and exported – under the trade name Guglip in the form of tablets and granules.

Because the preparation is a standardized extract of an Ayurvedic medicine developed as a modern medicine, it was designated by the licensee firm as an ‘allovedic’ drug.

The drug was well received and the demands shortly after its release showed an upward trend. Gugulipid was commercialized at 10 tonnes per annum and, from 1996 to 1997, its annual value was estimated at more than US\$80,000.

Based on the proceeds from these sales, CDRI received a good financial return in terms of royalty payments. However, the availability of the raw material, gum guggulu, became a major limiting factor in meeting the demand for the drug and its production was discontinued in July 1997. This demonstrates one of the limitations of pharmaceutical products derived from medicinal plants – the fact that many of the raw ingredients are still collected from the wild rather than from cultivated sources and, in many cases, these natural resources are becoming depleted and increasingly endangered.

Cultivation, as the following example of arteether derived from *Artemisia annua*, demonstrates, is one way round this problem. Another is to synthesise the active ingredient. Indeed, CDRI scientists have now developed a technique for manufacturing guggulsterones and the technology has been licensed to a company for commercialization.

## Antimalarials: $\alpha/\beta$ Arteether and Elubaquine

Malaria is a major health problem in many parts of the world, particularly southeast Asia, Africa and South America. So-called cerebral malaria, caused by *Plasmodium falciparum*, the most deadly form of malaria, is particularly difficult to treat and causes high mortality. Once the disease sets in, it progresses quickly. After the onset of coma, cerebral malaria patients are at high risk unless the disease is rapidly diagnosed and treated with fast-acting antimalarial schizontocides, which act against the stage of the parasite that multiplies in the blood cells. However, the available drug, chloroquine, is slow-acting. In addition, resistance of the malarial parasites to currently used antimalarial drugs, especially chloroquine, is widespread and increasing.

Since the 1980s, therefore, efforts have been made to develop fast-acting blood schizontocides for the control of multi-drug resistant malaria, and particularly cerebral malaria.

Among the promising candidates for such a drug is artemisinin, derived from *Artemisia annua* (family Asteraceae) used as an antimalarial in traditional Chinese med-



## HERBARIUM

• A herbarium is basically a museum for plants. Plant specimens are collected and preserved, usually by pressing and drying them, and stored in an organized fashion – like books in a library), and preserved for future study. CDRI has developed a specialized medicinal plant herbarium containing more than 5,000 voucher specimens together with a further 4,000 other plant specimens. The voucher specimens are of critical importance to research in medicinal plants as they allow the correct identification of species and are stored along with such details as when and where they were collected. The herbarium at CDRI is used by researchers to inventory the plants that occur in specific areas, to conduct original research on plants and to search for other plants related to a specific plant of interest. The herbarium is also a useful tool for botany students and even law enforcement agencies, which can use the specimens to help identify plants or plant parts found at the scene of a crime.

## FACILITIES

icine. Three chemical derivatives of artemisinin, namely artemether, arteether and artesinic acid, are very effective against multidrug resistant malaria parasites.

Against this background, CDRI scientists decided to investigate the potential of developing new antimalarials belonging to the artemisinin series with different modes of action.

The antimalarial drug, arteether, was developed in collaboration with the Central Institute of Medicinal and Aromatic Plants (CIMAP), a sister laboratory of CDRI in Lucknow.

CIMAP introduced *A. annua* into India and developed efficient agrotechnology for its cultivation. Initially, it was grown in the Kashmir valley and large quantities of artemisinin were produced.

Artemisinin is sparingly soluble in water or oil and not well absorbed by the gastrointestinal tract. CDRI scientists, therefore, made alterations to the chemical structure



## LIBRARY

• Even compared to libraries in research institutions in developed countries, the CDRI library has a more-than-adequate budget of some 17.5 million rupees a year (US\$350,000). This allows the library to subscribe to some 350 scientific journals, some of which are published monthly, others just once or twice a year. All of which adds up to some 7,000 new additions to the library each year. This vast resource, that dates back to the institute's foundation 50 years ago – and even beyond for some journals – is used not only by CDRI staff and students, but also scientists at the other CSIR institutions in Lucknow, including the Central Institute of Medicinal and Aromatic Plants (CIMAP), National Botanical Research Institute (NBRI) and the Industrial Toxicology Research Centre (ITRC). Researchers from further afield – even as far as south India – also make use of the CDRI library facilities, with students from many pharmacy colleges, for example, coming to consult the extensive journal collections. In addition to the collection of scientific literature housed on site, the CDRI library also offers search and downloading facilities of all the major scientific indexing internet services, including the popular PubMed and Medline.

Among the problems facing the CDRI library is one common to many libraries in institutions in developing countries. Compared to institutions in the North, journal subscriptions tend to be more expensive for institutions in the South because of the extra charges required to cover the cost of mailing the journals.



## FACILITIES

of artemisinin and prepared derivative compounds. Among these, arteether (the ethyl ether of dihydroartemisinin) was found to be superior to the other so-called 'semi-synthetic' derivatives because of its better bioavailability, lipophilicity, pharmacokinetic properties and reduced toxicity.

The conversion of artemisinin to arteether is a two-step process that produces a 30:70 mixture of  $\alpha$ -arteether, an oily substance, and  $\beta$ -arteether, which is crystalline. Because both  $\alpha$ - and  $\beta$ -arteether have similar efficacy against malarial parasites. Therefore, mixture of  $\alpha$ - and  $\beta$ -arteether was designated  $\alpha/\beta$  arteether and developed as a drug jointly by CIMAP and CDRI.

After the necessary pre-clinical pharmacological and toxicological studies,  $\alpha/\beta$  arteether was successfully used in clinical trials to treat some 500 malaria-infected patients at seven centres throughout India.

A distinguishing feature of  $\alpha/\beta$  arteether is its rapid action against the blood schizont stage of the malaria parasite present in the blood. In a three-dose regimen, it is able to cure multi-drug resistant *P. falciparum* malaria. Marketed under the brand name E-mal, it is now the drug of choice for treating comatose cerebral malaria cases. Arteether can also block the transmission of malaria by virtue of its effect on another of the malaria parasite's life-cycle stage, the gametocytes, which are present in the blood and ingested by feeding mosquitoes. E-mal, therefore, is a good alternative to the widely used primaquine for controlling *P. falciparum* transmission in drug sensitive/resistant areas.

The second CDRI antimalarial drug, elubaquine, which entered the marketplace in 2000, is an example of a purely synthetic compound. It is also a good alternative to primaquine, being several times less toxic, and is particularly active against tissue-stage malaria.

## Product pipeline

Competing with multinational drug companies – albeit on a much smaller scale – requires not only a successful portfolio of products, but also a strong ‘product pipeline’. In many ways, the strength of a research institution such as CDRI should not be measured so much in terms of its products, but more in terms of what it is currently developing and has the potential to produce in both the near-future and the long-term. Using such a measure of success, CDRI stands alongside the best institutions in the developing world and competes favourably with many institutions in developed countries.

“We have several products in the pipeline,” confirms C.M. Gupta. “The most advanced of these is a lipid-lowering compound, 80/574, which is currently undergoing phase III clinical trials.”

Among the other compounds under development are:

- Picroliv – which protects the liver against damage from drugs and diseases such as hepatitis. It is currently undergoing clinical trials.
- Another antimalarial compound is just entering phase I clinical trials and has attracted the interest of commercial companies.
- An anti-ischaemic compound, derived from a herbal remedy, that controls the damage caused by a stroke is just entering toxicological trials.
- Two compounds that target osteoporosis.
- A wound healing compound.
- An anti-ulcer compound.
- Good lead compounds have also been identified for the treatment of Alzheimer’s diseases and stress.

In addition, two traditional remedies for diabetes that act by reducing sugar levels in the blood have entered clinical trials.

“These are regarded as modern drugs even though they are composed of a collection of components, perhaps three or four, rather than a single component,” explains Sat-awayan Singh. “They are still standardized.”

“But variation between samples needs to be standardized, too,” adds Asthana, “so that we can control the dose of the active substance.”

“*Over the past five years, the Indian pharmaceutical industry has shown an annual growth of more than 20 percent, twice the world average.*”

# Research Partnerships

“Unless we network as a ‘virtual institute’ we will never be able to compete with the multinationals,” says C.M. Gupta, referring to CDRI and its sister institutes in the CSIR system. “We are currently involved in several programmes that could be called ‘India Ltd.’”

One of these is a collaborative project being carried out between 18 CSIR laboratories based on traditional knowledge. The project aims to make an inventory of microbes, plants and other organisms that have been used in healthcare by the Indian people, including the plants used in Ayurvedic medicine, for generations.

International agreements give nations sovereign rights over their indigenous biodiversity. However, this is not always respected and ‘biopiracy’ – the patenting of a nation’s biodiversity by commercial companies, often those from developed countries – continues to be a problem for many developing countries. In one high-profile case, for example, researchers at a US university were granted a patent in 1995 that covered the wound-healing properties of turmeric, a plant indigenous to India and used for centuries to treat wounds and rashes. The Indian government – through CSIR – challenged the patent and, in 1998, the US Patent and Trademark Office ruled in favour of the ‘prior art’

of the Indian people and revoked the patent. The documentation of such indigenous knowledge being carried within the CSIR system should be enough to protect traditional medicines from similar illegal moves.



Another collaborative project has evolved from the Indian government's decision in 1981 to create the Department of Ocean Development. The aim of this move was to help create a deeper understanding of the Indian Ocean and to develop technologies for harnessing its resources. Under the New Millennium Indian Technology Leadership Initiative (NMITLI), twelve CSIR laboratories, mainly located in coastal areas of India, are involved in a project to sample and survey marine flora and fauna. CDRI is also involved in the NMITLI project with the specific role of screening unusual compounds from these organisms for potential medical use.

CDRI is developing a collection of marine flora and fauna. Many extracts of these organisms have been made for future screening, explains Ram Raghbir, head of CDRI's pharmacology division.

"The success of any programme designed to identify novel lead compounds depends on the width of the net," explains Raghbir. "That is why we are looking at a range of plant materials, including traditional herbal medicines, as well as marine life."

Several products from CSIR's exploration of the sea are showing promise in fighting cancer and controlling blood lipid levels. In addition, a potential antidiabetic preparation has entered phase I clinical trials.

Closer to home, CDRI carries out collaborative research and development projects with institutions in and around Lucknow. Among these was the development of the anti-malarial drug, arteether, in collaboration with the Central Institute of Medicinal and Aromatic Plants (CIMAP) described above (see page 38). CIMAP scientists developed the agrotechnology for the cultivation of *Artemisia annua* in India and refined techniques for the isolation of artemisinin from the plants and the process technology for the production of semi-synthetic arteether. CDRI scientists, on the other hand, developed the procedure for converting artemisinin to arteether and performed all the necessary pharmacological and clinical tests that enabled the compound to be registered as an antimalarial drug.

"We also carry out clinical trials with the assistance of King George's Medical Hospital here in Lucknow and Bombay Medical Hospital," adds C.M. Gupta. "The other collaboration we have, as I've explained before (see page 31), is with Jawaharlal Nehru University in New Delhi. We provide coursework for their students while the university awards the degrees."

# Commercial Partnerships

In parallel with its research and development collaborations, CDRI has entered into contracts with a collection of commercial partners, both in India and overseas.

“For example,” says Chandan Singh, head of the Medicinal and Process Chemistry Division, “we have been working with the Danish company Novo Nordisk, a global leader in diabetes care, for four years now and together we are developing several interesting leads.”

The list of national companies that have entered into drug development and commercial agreements with CDRI reads like a ‘who’s who’ of the Indian pharmaceutical industry. Nicholas Piramal India Ltd (NPIL), for example, is among India’s leading pharmaceutical companies, with net sales of 12.7 billion rupees (US\$254 million) and a net profit of 1.9 billion rupees (US\$38 million). CDRI and NPIL have been working together since 1998 and are developing two products – the antimalarial bulaquine (marketed as Aablaquine) and an antidiabetic derived from a herbal preparation.

“The CDRI collaboration functions well,” confirms NPIL’s Juliet Toyson. “It provides good expertise and many facilities under one roof, which gives confidence that such collaboration has a value.”



“ *Establishing a drug manufacturing plant is 40 percent cheaper in India compared to developed countries and the cost of bulk drug production is 60 to 70 percent less.* ”

Such public-private partnerships are not new to CDRI. Indeed, collaborations with such companies as Hindustan latex Ltd, run by India's Ministry of Health and Family Welfare, and Themis Medicare Ltd, Mumbai, date back 14 and 20 years respectively.

“Since 1991, we have been marketing Centchroman, a once-a-week oral contraceptive that has many advantages over conventional steroidal contraceptive pills,” says A.G. Sankaran, deputy manager of Hindustan Latex. “Developed by CDRI, this product has increased the competitive advantage of our company.” Hindustan Latex have also just begun marketing a second product developed by CDRI, the spermicidal Consap.

A survey of some of CDRI's commercial partners turned up some negative comments along the lines of: “Things don't move fast enough,” and: “Being a government institute, some set rules need to be followed that, at times, may not be the best for business.” However, the positive responses far outweighed the negative. Among these, were the comments from Lumen Marketing Company, Chennai, which has been collaborating with CDRI since 2001 in marketing the memory-enhancing ProMind. “Through this collaboration, our company gains credibility in the crowded herbal medicines market,” say Lumen. Indeed, every pack of ProMind bears the phrase: “a prestigious product of CDRI,” and the CDRI name is highlighted in all the company's promotional campaigns.

In general, most of the companies surveyed also worked with other institutions and research partners, but all were satisfied with CDRI's input into their programmes and either continue to develop products with CDRI or are actively searching for new collaborative opportunities with the institute – sure signs that CDRI is providing the right kind of service to India's up-and-coming pharmaceutical industry.

# Strengths and Weaknesses

Such long-established and on-going collaborations with the commercial pharmaceutical sector indicate that CDRI is doing many things correctly.

Factors that contribute to CDRI's continuing success are highlighted as the institute's strengths in Table 4. Among these are long-term government funding, the presence of a range of scientific expertise that covers the whole process of drug discovery through to commercialization, and well-maintained support structures such as the animal house and library.

However, as a research organization in a developing country – albeit one of the more technologically advanced countries in the South – there is still plenty of room for improvement.

CDRI's director, C.M. Gupta, agrees. "We have identified several areas where we can do better," he says, "and we are working on correcting these. However, there are also some areas where our problems are symptoms of the wider Indian society. Unfortunately, we can do nothing about these."





One of the problems that has been tackled successfully is common to many developing countries – an unreliable power supply. To counter this, CDRI has installed backup generators that kick in after two or three minutes if there is a power blackout. With some sensitive scientific equipment, however, an interruption in supply of even a fraction of a second can cause the instrument to fail. At CDRI, such machines are connected to special equipment that provide an uninterrupted power supply (UPS) that can run for up to 30 minutes. “This is an effective solution,” says Gupta, “but it adds to the cost of buying and maintaining new equipment.”

*Table 4. CDRI's strengths and weaknesses*

### **Strengths**

- Long term government support and funding.
- Being part of a larger overall research structure allows 'networking'.
- A defined mandate, regularly updated through a government appointed committee, leads to focused research.
- Departmental organization allows research to cover the whole 'chain' from drug discovery to clinical trials and patenting – and allows specialization in areas of expertise.
- Support structures, e.g. library, animal house, herbarium, are all in place and well maintained and funded.
- Well-trained staff – most have received training in the US or Europe. Extra training is provided if required, e.g. management skills for heads of departments.
- Increasing focus on high impact factor publications improves both the institution's and the scientists' 'visibility'.
- Collaboration with industry allows royalties to feed back into the research and development budget.
- Scientists can tap into the traditional knowledge base.

### **Weaknesses**

- Slow to take up new techniques and obtain new equipment – a situation exacerbated by the high cost of equipment and reagents.
- Unreliable electricity supply.
- Computer infrastructure is weak – especially for such a large organization.
- Limited opportunities for international travel and scientific interactions.
- Expansion and modernization is limited by old (18th century) building infrastructure.
- Humidity, dust and even rodents cause problems for equipment.
- Poor technical support for servicing and repairing equipment.

Among the problems that Gupta and his staff have learned to live with – at least for the moment – are the restrictions placed on their activities by the building that houses the institute, the 18<sup>th</sup> century Chattr Manzil Palace.

“This limits expansion and modernization,” admits Gupta. “Due to the building’s historical importance, for example, we cannot drill through the walls – which in any case are more than 2 metres thick – to pass through the cable needed for our computer network. Thus our information technology infrastructure is weak, especially for such a large organization.”

Despite these constraints, the outlook is promising. “A new state-of-the-art campus is currently being developed and will be ready for us to move into in 4 or 5 years’ time,” confirms Gupta. “Of course, a modern computer network will be an integral part of the infrastructure.” Until then, students and researchers alike have to make do with a computer network node in each division and a cluster of 30 internet-connected computers in the institute’s library (see box on page 40).

Although in some ways the situation at CDRI is artificial – compounded by the building’s historical importance – this lack of access to internet and e-mail facilities, and the ‘connection’ they provide to the wider scientific community, is typical of many research institutions in developing countries.

The so-called ‘digital divide’, however, is just one factor that isolates scientists in developing countries from one another and their counterparts in the North. Limited opportunities to travel and attend international meetings are another. “Yes, funds for travel are limited,” agrees Gupta, “but grants are available and, typically, the best researchers are able to access these.”

“What is really a major problem is the poor technical support for servicing and repairing equipment,” says Gupta. “Although some agencies are very prompt, others are totally unreliable. Sometimes complaining about a local representative to the head office of an international company produces results, but sometimes even this doesn’t work.”



# Conclusions

India currently spends about one percent of its gross national product (GDP) on research and development. Although this is relatively high compared to many other developing countries (neighbouring Sri Lanka, for example, spends only 0.16 percent of its GDP on research and development), India's research and development budget is only at the minimum level recommended by the Vienna Plan of Action, put forward by UN organizations some 30 years ago. In comparison, most developed countries commit between two and three percent of their GDP to their research and development budgets.

However, India's economy has grown at a rate of more than seven percent each year for the past ten years. This has meant sizeable increases for the national research and development budget, much of which is channelled through CSIR and its 38 institutes, including CDRI.

Against this background of increasing public funds for research and development, investment in scientific research has tended to take a back seat amongst Indian pharmaceutical companies, which have tended to produce large quantities of generic drugs. To remain competitive – and to face up to new challenges set by changes to patent rules endorsed by the World Trade Organization (WTO) in 2005 – Indian companies must begin to re-focus and invest heavily in research and development.

CDRI's track record of blending traditional knowledge of medicinal plants with cutting edge chemistry and pharmacology puts the institute in a strong position for collaborating with private companies. Indeed, as highlighted by Zaka Imam, head of the Technical Information, Industrial Liaison and Planning Division (see page 27), CDRI tries to link each project with a business development objective, a sponsored or collaborative project, or a commercial product.

CDRI's existing expertise and scientific infrastructure, together with the large and highly educated workforce present in India, gives the institute a competitive advantage when competing for such research and development contracts with private companies. Indeed, pharmaceutical companies from developed countries entering into collaborative agreements with CDRI know that the research they require can be carried out at costs much below those in the North. For example, it is estimated that it costs US\$1 billion in research and development to bring a new drug to the market in developed countries, whereas Indian research organizations can do it for just US\$50 million.

Such issues present both challenges and opportunities to CDRI – as well as other institutions in the South working in a similar area. CDRI is poised to take full advantage of these challenges and opportunities.



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## TWAS

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## TWAS

TWAS, the academy of sciences for the developing world, is an autonomous international organization that promotes scientific capacity and excellence in the South. Founded in 1983 by a group of eminent scientists under the leadership of the late Nobel Laureate Abdus Salam of Pakistan, TWAS was officially launched in Trieste, Italy, in 1985, by the Secretary General of the United Nations.

TWAS has more than 800 members from 89 countries, 85% of whom live and work in developing countries. A Council of 13 members is responsible for supervising all Academy affairs. It is assisted in the administration and coordination of programmes by a small secretariat, headed by the Executive Director. The secretariat is located on the premises of the Abdus Salam International Centre for Theoretical Physics (ICTP) in Trieste, Italy. UNESCO is responsible for the administration of TWAS funds and staff. A major portion of TWAS funding is provided by the Ministry of Foreign Affairs of the government of Italy.

The main objectives of TWAS are to:

- Recognize, support and promote excellence in scientific research in the South.
- Provide promising scientists in the South with research facilities necessary for the advancement of their work.
- Facilitate contacts between individual scientists and institutions in the South.
- Encourage South-North cooperation between individuals and centres of scholarship.

To achieve these objectives, TWAS is involved in various activities and collaborates with a number of organizations, especially UNESCO, ICTP and the International Council for Science (ICSU). For additional information, see [www.twas.org](http://www.twas.org).

## THE DAVID AND LUCILE PACKARD FOUNDATION

The David and Lucile Packard Foundation was created in 1964 by David Packard (1912-1996), co-founder of the Hewlett-Packard Company, and his wife, Lucile Salter Packard (1914-1987). Throughout their lives in business and philanthropy, the Packards sought to use private funds for public good.

Guided by the founders' values, the David and Lucile Packard Foundation supports both people and organizations with the aim of enabling the creative pursuit of science; conserving and restoring the Earth's natural systems; improving the lives of children; and advancing reproductive health.

For additional information, see [www.packard.org](http://www.packard.org).





## EXCELLENCE IN SCIENCE

This series of booklets – published by TWAS, the academy of sciences for the developing world – highlights successful scientific institutions in the South and explains how their research has both been sustained over a number of years and is helping their host nations achieve sustainable economic development.