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CHANGING PARADIGMS OF INFECTIOUS DISEASES IN DEVELOPING COUNTRIES

New Paradigms of Infectious Diseases

Microbes and man have been engaged in a continuing battle for ascendancy on this planet. In India whatever successes had been achieved on the public health front were largely in the field of infectious diseases. Small-pox is an excellent example. To this will soon be added elimination of polio, guineaworm disease, tetanus in the newborn and leprosy. Despite these successes, the microbial front remains disturbing and is a cause of anxiety. Thirty new diseases have appeared on our planet in the past 20 years. Infectious diseases continue to be the leading cause of death. What diseases were thought to have been conquered or nearly-conquered, have now staged a comeback. Examples are plague, malaria and kala-azar. Diseases such as tuberculosis thought to be controllable through available technologies and for which elaborate national plans of control were developed decades ago, still exist and are getting worse. What has proved to be a new and deadly disease of mankind throughout the world and despite its early recognition soon after its introduction into India in 1985-86, HIV infection in India is rising inexorably and there is a sense of despair. Diseases such as dengue and cholera which are endemic in India with periodic outbreaks from time to time, have now assumed more virulent characteristics. These examples represent a formidable array of emerging and re-emerging infectious diseases and a new paradigm of infectious diseases is now in evidence due to a multiplicity of factors. Recognition of these paradigms and the factors contributing to them is essential for developing effective control programmes. The increasing phenomenon of drug resistance is a part of the paradigm.

Amongst the factors influencing the new paradigms of infectious diseases, there is the age-old factor of poor living conditions which in many areas have worsened for certain sections of the community, often in spite of growing overall economic prosperity.

Other factors include the unintended effects on ecology, at both macro and micro levels, resulting from human activities under the overall rubric of "development". These developmental activities include:

(i) Dams and irrigation projects which are necessary and bring about prosperity may also tend to create ecological conditions, if not foreseen, conducive for re-emergence of old diseases, especially vector-borne diseases.

(ii) Industrialisation and energy-producing initiatives which are necessary for economic growth but also lead to environmental degradation with health consequences.

(iii) Changes in land use patterns and human encroachments of forest areas, a common phenomenon today, exposing human populations to infections with which they have had no previous encounter.

(iv) Unplanned urbanisation and excessive population growth creating optimal conditions for the entry and spread

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of infectious diseases in congested squatter settlements. The essential problem here is the breakdown of infrastructure and services in slum areas creating conditions conducive to the resurgence of diseases once brought under control. Urban health is a matter of overwhelming urgency without much time left to correct the prevailing deficiencies and hazards.

(v) Growing trade, tourism and trucking accompanying increased international travel leading to greater intermingling of people today than ever before creating conditions for the spread of infectious diseases. The speed of transmission of infections increased enormously as mankind transited from sailing ships to jet planes.

The changes in climatic conditions now reveal significant health effects. Atmospheric pollution, deforestation and ozone depletion play a key role in global warming. This in turn, would lead to higher surface water evaporation rates with greater rainfall and heavier monsoons in key areas of the planet. This would alter everything from migration of birds, habitat ranges of insect vectors of disease and the availability of arable land for agriculture. Dengue and malaria transmitting vectors are sensitive to rainfall and ambient temperatures. As a result of global warming, malaria may spread further up the foothills of the Himalayas. The lesson of macro-ecology is that all life forms and chemical systems are closely linked in complex ways[1]. It would appear that current and anticipated changes in local and global ecologies would favour some microbes and their insect vectors.

In place of the Cold War there are now multiple local wars and conflicts which along with natural disasters, such as famines and floods, lead to mass movement of people internally within countries and across borders. The living conditions of the refugees provide a fertile ground for infectious diseases.

Changes in human lifestyles and behaviour including sexual behaviour and food habits are another potent factor in the changing paradigms of infectious diseases. Lastly, the continuing inadequacy in the quality and outreach of health services is an important factor compounding the situation.

The challenges presented by the New Paradigms of Infectious Diseases can be conveyed by the following four diseases.

Dengue

Dengue, by the 14th of October 1996, had caused 126 reported deaths and 2,545 cases of presumed dengue fever complex admitted to public hospitals giving a mortality rate of 5 per cent. While this corresponds to the average rate of mortality in other parts of the world, there may be scope for it to be reduced further by improved case management through early recognition of haemorrhagic manifestations and shock, prompt and efficient replacement of lost plasma through fluids and electrolytes, plasma/plasma expanders and platelets as indicated. Blood transfusion will be needed if there is internal bleeding. The modern regimen of treatment of Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) was evolved by Thai physicians, some years back and now forms the basis of WHO recommendations[2]. This regimen has been shown to reduce the mortality rate to 2.0 per cent or less.

Dengue had been known to be endemic for over two centuries in India and for the most part had been running a benign self-limited course. All the four known serotypes of the dengue virus are now known to be in circulation. The disease has lately changed its course manifesting itself in a proportion of cases in a severe form of the disease, DHF/DSS. This new lethal manifestation of an old benign disease broke out in Manila in the Philippines for the first time in 1953; then attacked Bangkok in Thailand in 1958; Havana, Cuba experienced the worst DHF known to mankind in 1981. DHF had been raging in our immediate neighbour Myanmar since 1970. Cambodia had seen a severe outbreak of DHF last year. In Manila, dengue occurred each year after the rains. Seasonal and cyclical epidemic pattern of dengue with DHF/DSS in a proportion of cases is a recent phenomenon developing in India and Sri Lanka in the same manner as happened in the Philippines, Thailand and Indonesia. In other words, there has been a westward movement of this new paradigm into India, Pakistan, Sri Lanka and Maldives in the 1980s and early 90s in which Dengue 3 (DEN-3) had been the predominant serotype. The history of Indian dengue illustrates the well known transition from a paradigm of small outbreaks to a paradigm of major outbreaks with DHF/DSS[2-4]

The new dengue disease paradigm has now secured a firm foothold in India. The paradigm is manifesting itself extensively in Latin America and the Caribbean since last year. Its emergence as a major health problem has been most dramatic in the American region. This region had an excellent record of eradicating *Aedes aegypti* in the 1950s and 60s as a part of the Yellow Fever Control Programme, but with the discontinuation of this Programme from the 1970s, Aedes returned, and the worst ever outbreaks of dengue are now raging there. This shows that even a year's slackening of vector control measures could bring back outbreaks of

vector-borne diseases. Similarly, relaxation of immunisation can result in re-emergence of disease as in the Russian Federation and the former USSR with respect to diphtheria. Aedes is a very efficient epidemic vector of both dengue and yellow fever[3,4]. The virus type responsible for the current outbreak in Delhi has not yet been identified but work in this area is going on.

The reasons for this dramatic emergence in India and around the globe of dengue/DHF as a major public health problem, as already indicated, are many: Ineffective mosquito control programme, major demographic changes–the most important being uncontrolled urbanisation, excessive population growth and urban decay characterised by substandard housing and inadequate water and waste disposal system. Increased travel by airplanes produces constant exchange of dengue viruses.

There is a crisis approach to public health in our country, public health activities being largely punctuated from crisis to crisis. What is needed are sustained programmes for the prevention of epidemic transmission. Surveillance systems are inadequate as the Technical Advisory Committee's (TAC) Report on Plague demonstrated. Mosquito densities in relation to rainfall and ambient temperatures are not available and early detection and reporting systems are inadequate. No dengue vaccine is available although a quadrivalent attenuated live vaccine representing all four serotypes has been developed in Thailand and is in advanced stages of trial. This vaccine appears to be safe and effective but it will probably be another 5 years before an effective dengue vaccine will be available for public use. Prospects for reversing the recent trends in dengue/DHF do not look bright in Delhi and early breakthroughs may not happen. And yet, there is no cause for despair.

In response to the recommendation of the TAC on Plague, a National Apical Advisory Committee for Disease Control through Surveillance and Response has been established by the Government. Treatment regimens have been developed with respect to dengue[2], control of the disease is possible through efficient management of the disease and through a double-pronged attack on mosquito vectors, namely, insecticide spraying by Government action and elimination of mosquito breeding by family and community action to reduce sources of larval breeding. The latter strategy is particularly important, especially in the long run and one would like to see social mobilisation efforts in much greater evidence.

The most effective means of dengue vector control is environmental management through physical transformation of largely man-made vector habitats, within and around human dwellings. Education and community participation in planning, execution and evaluation of these control measures is the critical factor. Commonsense approach is needed. Aerial spray is often used, where extensive areas must be treated in a short period, but spectacular results may not be expected as the Aedes rests indoors. The approach must be complemented with larvicidal application in and around homes where containers cannot be emptied or covered. The most effective way to control Aedes is larvicidal source reduction by eliminating clean water holding containers that serve as larval habitats[4]. The 1981 Aedes eradication campaign in Cuba depended upon reduction of larval habitats in artificial and natural containers of water, intense public education, and biological and chemical control methods. The Tanzanian campaign consisted of source reduction, education and clean-up campaigns. Dengue control is an area where Science and Society meet. There is considerable expertise on this aspect within the ICMR in India which must be mobilised.

Pro-active, laboratory-based surveillance systems that can provide early warning of an impending dengue epidemic must be developed. An encouraging development is the Thai dengue vaccine which could be available in the next few years. Another possibility is the use of genetically engineered mosquitoes which cannot transmit the disease.

Malaria

After the initial successes India is now unable to get the upper hand in malaria control and over the past decade or so the number of malaria cases has remained unchanged with the addition of increase in falciparum malaria. The issue today is that malaria has now entered new ecological niches[5]. The problem is essentially due to man-made environmental alteration which provides excellent opportunities for the mosquito vector to breed. The new paradigm of malaria consists of new eco-types such as irrigation malaria, urban malaria, development project malaria, migration malaria and border malaria[5]. These eco-types are in addition to the already existing eco-type of rural malaria in rain-fed areas. Environment degradation is conducive to the sustenance of malaria. Epidemics are increasingly common such as that currently in Mewat, Haryana. The revised malaria strategy consists of early diagnosis and prompt treatment and focuses on local transmission dynamics and control based on selective and sustainable technologies. But there is a wide gulf between the fine experimental projects involving source reduction through biotechnological methods and their extension into nation-wide malaria control programmes.

Malaria was one of the first infectious diseases to be treated successfully with the drug, quinine, extracted from the bark of the cinchona tree. The latest and highly effective anti-malarial compound is also derived from plants– *Artemisia annua* L.–for chloroquine resistant malaria. Forty per cent of the world's population is still at risk and is yearning for a vaccine, cheap and effective. There is not much private investment in malarial research throughout the world and most of the work is done under Government sponsored and charity auspices. Drug resistance is a real problem and hence the different strains in different geographic areas may require different drugs. It is disappointing that the antimalaria vaccine developed by Dr. Manuel Patarroyo, has now been shown to be not effective. There were initial successes with this vaccine, but only partially to the extent of 31-34 per cent protection but more recent studies in the Gambia and Thailand confirm the failure of the vaccine. The Patarroyo vaccine is a harbinger of better vaccines to come based on multi-stage antigens.

Cholera

A completely new strain of cholera vibrio had emerged in India in 1992 in Madras. It has been christened *Vibrio cholerae* 0139 Bengal, with pandemic potential. It produces a clinical picture of severe disease, dehydration and hyponatraemia similar to classical cholera but is susceptible to some antibiotics. It has spread throughout India and went to Bangladesh in 1993 and then on to South West China, Thailand and other parts of South-East Asia. What happens to the Vibrio in between the outbreaks is not known and some scientists had postulated that the Vibrio is dormant between outbreaks in the Hilsa fish in the Hooghly. No confirmatory evidence had been forthcoming for this hypothesis but algal blooms have been found to be responsible for the spread of El tor cholera to Latin America in 1991, a continent that had not experienced cholera over the last 100 years. Algal blooms where cholera organisms reside, are, in effect, "giant floating gene pools" in which antibiotic resistance, virulent genes and plasmids move about freely between viruses and bacteria. In the paradigms that are being discussed, marine eco-systems influencing human health should find an important place. It would appear that current and artificial changes in global ecologies favour microbes and their insect vectors.

Tuberculosis

With the increase in the incidence of AIDS, tuberculosis is becoming worse. The efficacy of BCG vaccine in preventing tuberculosis remains variable depending upon geographical and epidemiological factors. A better vaccine than BCG is needed although the disease is still treatable with existing technologies just as HIV/AIDS is preventable. India has not derived maximum benefits from the results of research at the Tuberculosis Research Centre in Chennai with respect to multi-drug and domiciliary therapy, though it is now proposed to use short course multi-drug therapy against tuberculosis throughout the country. Case management with such a therapy, case finding with high quality bacteriological examination, improved programme management and directly-observed treatment can lead to a virtual cessation of transmission of tuberculosis in the general population even under adverse conditions.

DNA Vaccines

Multi-drug resistance is rapidly advancing in India and gradually assuming serious proportions. New drugs and new vaccines are needed to fight tuberculosis effectively. It is noteworthy that mice injected with plasmid DNA encoding a single mycobacterial antigen (65 kDa) developed immunity against subsequent challenge with the tubercle bacillus. It seems likely that a DNA vaccine against tuberculosis might replace the BCG. In animal models of several infectious diseases, DNA vaccines seem to be broadly applicable for conferring protective immunity to a number of infectious pathogens. They seem not to need replicating vectors and adjuvants and seem to be practical and safe. Eventually, a cocktail vaccine, DNA plasmid-based may be needed encoding for a number of mycobacterial antigens to generate complete and lasting protection against tuberculosis.

DNA vaccines may help man to be one step ahead of microbial pathogens which are either staging a comeback or evolving into more virulent organisms. Surely, the biological front is never static. To foresee is to govern.

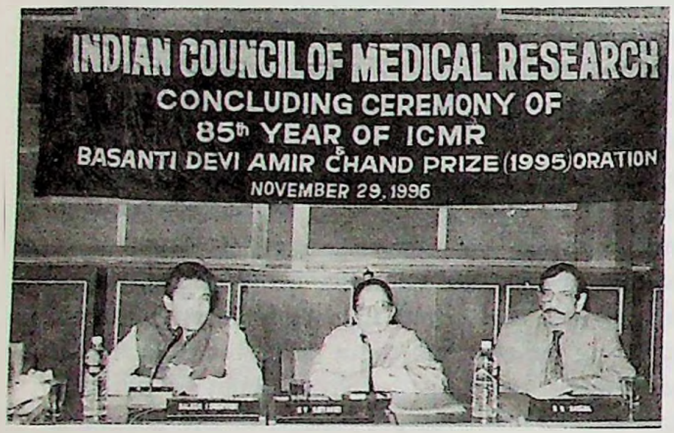
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The write-up is based on the Second Dr. B.R. Ambedkar Centenary Award (1993-94) Oration of the ICMR delivered by Dr. V. Ramalingaswami, National Research Professor. All India Institute of Medical Sciences, New Delhi, on October 15, 1996 at New Delhi.

EIGHTY FIFTH ANNIVERSARY CELEBRATIONS OF ICMR CONCLUDED

The year long celebrations of the 85th Anniversary of the Indian Council of Medical Research concluded in November, 1996. Shri Saleem I. Shervani, Hon'ble Minister of State for Health and Family Welfare and President of the Governing Body of ICMR presided over the concluding ceremony organised at the National Science Centre. New Delhi on November 29 1996.



Shri Saleem I. Shervani, Hon'ble Minister of State for Health and Family, Welfare and other dignitaries on the dias.

The Basanti Devi Amir Chand Prize (1995) Orations of the ICMR were also delivered on the same day. The joint winners of this Prize *viz.*, Prof. N.K. Ganguly, Head, Department of Experimental Medicine and Biotechnology, and Prof. R.C. Mahajan, Head, Department of Parasitology, Postgraduate Institute of Medical Education and Research, Chandigarh, delivered these orations respectively on Pathophysiology of Bacterial Diarrhoea and Pathophysiology of Parasitic Diarrhoea.



Basanti Devi Amir Chand Prize awardees and other dignitaries on the dias.

The Delhi based ICMR Institutes/Centres (*viz.* Malaria Research Centre, Institute of Pathology and Institute of Cytology and Preventive Oncology) as also the National Institute of Nutrition, Hyderabad had



Dr. N.K. Ganguly and Dr. R.C. Mahajan delivering their oration.

organised an exhibition on this occasion, comprising posters, charts, photo-panels on major health problems like malaria, cancer, AIDS, dengue, rheumatic heart disease, *etc.* and their prevention and control; bioenvironmental control of mosquito vectors;



Visitors at an exhibition organised at the function.

nutritional deficiency diseases and their prevention with the help of balanced diets/foods prepared from locally available food items, *etc.* There was a live demonstration of larvivorous fishes feeding on mosquito larvae, apart from specimens of organs with malignant (cancerous) lesions. Video films on various health problems (like malaria, nutrition, *etc.*) were screened and health

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Visitors at an exhibition organised at the function.

education material in the form of folders, pamphlets, booklets and brochures brought out by various ICMR Institutes/Centres were distributed.

The Hon'ble Minister released a special issue of the ICMR Bulletin (November 1996) on this occasion, highlighting reports of the year long celebrations. Shri Shervani also presented mementos to the former Directors-General and also the Additional Directors-General present on the occasion.



Hon'ble Minister releasing the special issue of the ICMR Bulletin.

Welcoming the Hon'ble Minister of State for Health and Family Welfare and other dignitaries who attended the function, Dr. G.V. Satyavati, Director-General, ICMR, gave a brief overview of the significant contributions of the Council over the last eight and a half decades and referred to milestones such as the establishment of the ICMR as the Indian Research Fund Association in 1911 and publication of the Indian Journal of Medical Research (1913)–the first Indian journal exclusively devoted to medical research; institution of various awards by the Council (1953); constitution of the first Reviewing Committee (1966); as also the second Reviewing Committee (1982-83); and the phase of expansion of the Council in the late seventies and the eighties through the setting up of Regional Medical Research Centres, *etc.*

She also drew attention to the various bottlenecks encountered by the Council over the past several years that need the urgent attention of the policy makers in the Government, such as poor funding, and lack of autonomy (which was pointed out by the First Reviewing Committee itself). This Reviewing Committee had categorically stated that these two critical factors had affected the efficiency and performance of the Council. The second Reviewing Committee of the ICMR had also recommended greater autonomy, better funding as also better service facilities for ICMR staff. She informed that as much as 80 per cent of the budget allocated goes towards payment of salaries, with little left for research. Extramural support to scientists in Medical Colleges which was once considered a strong point of the ICMR for nurturing the research talent in the biomedical field in the country, has dwindled from about 60 per cent during 1970s to barely 25 per cent now. She noted that although ICMR is the oldest Research body in India, currently it has a lower fund allocation than the youngest S&T Department *viz.*, Department of Ocean Development (DOD).

Addressing the distinguished gathering, Shri Shervani congratulated the ICMR and its scientists for their dedicated efforts. He called upon the Council's scientists to rededicate themselves to high quality research and to ensure that the ICMR reaches greater heights in the coming years and joins hands with health authorities to find practical solutions relevant to the health problems of our country. A very important challenge before all medical scientists and health authorities, he said, is to find appropriate ways and means to ensure practical application of the outcome of important medical research and that too without loosing much time, which requires not only interaction among multiple groups involved in the health and development sector in the country but also coordination at the highest levels.

Shri Shervani said "The ICMR has come a long way in this span of 85 years. Its research activities range from the conventional disease-oriented studies through intramural research (initiated in the early part of this century)—as relevant to a tropical country like India—to the current multi-disciplinary approach to newer



Hon'ble Minister of State for Health and Family Welfare delivering the presidential address.

dimensions of various health problems encountered by our country".

Shri Shervani further added "In its 85 years of existence, ICMR has always tried to assist health authorities in case of various situations arising in health sector in India—be it epidemics like cholera, plague, dengue, hepatitis, *etc.* or aflatoxicosis or even man-made disasters like the Bhopal gas tragedy. The ICMR (and its Institutes) have either been approached by the State/Central Health Departments or the Council itself has offered such assistance to the State and Central Health Authorities by means of field visits, and aiding in diagnosis and management".

He felt "While ICMR has many successes in its 85 years of existence, there are many new challenges the Council has to face. What the ICMR needs today is not only adequate funding but also focussing on specific problems and also build on its strengths. With the advent of newer research agencies like the Department of Biotechnology and the industry-oriented research agencies like CSIR which are likely to come up with more and more products—be it diagnostic probes/kits or vaccines and other products (including drugs) that will need authentic evaluation, ICMR has to gear itself to provide vital support for such evaluation, on a massive scale".

ICMR NEWS

Meetings of the Scientific Advisory Groups (SAGs)/ Scientific Advisory Committees (SACs) held at New Delhi:

SAG of the Division of Basic Medical Sciences	January 3, 1997
SAC of the ICMR-NIC Centre for Biomedical Information, New Delhi	January 14, 1997

Meetings of the Project Review Committees (PRCs)/ Expert Groups/Committees held:

PRC on HIV/AIDS and Substance Abuse	December 10, 1996 (at Calcutta)
PRC on Malaria, Filariasis, Leishmaniasis and Diarrhoeal Diseases	December 12, 1996 (at New Delhi)
PRC on Tuberculosis and Leprosy	December 13, 1996 (at New Delhi)
Expert Committee on ENT	December 23, 1996 (at Madurai)
Meetings of Experts and Investigators on (i) Traditional Remedies for Bronchial Asthma, and (ii) Filariasis	December 30, 1996 (at New Delhi)

Participation of ICMR Scientists in Scientific Events:

Dr. A. Roy Chowdhury, Dy. Director, Regional Occupational Health Centre (Eastern), Calcutta, participated in the II International Conference on Environmental and Industrial Toxicology at Bangkok (December 9-13, 1996).

Dr. C.N. Paramasivan, Dy. Director (Sr. Grade), Tuberculosis Research Centre, Chennai, participated in the Annual Conference of the Sri Lanka College of Microbiologists at Colombo (December 13-15, 1996).

** ** **

Dr. M.D. Gupte took over as the Director of the Institute for Research in Medical Statistics, Chennai w.e.f. December 11, 1996.

** ** **

Dr. S.K. Kashyap, relinquished charge as Director, National Institute of Occupational Health, Ahmedabad w.e.f. October 31, 1996.

Dr. M. Mohan Ram relinquished charge as Director, National Institute of Nutrition, Hyderabad w.e.f. December 31, 1996.

ICMR AIDED SYMPOSIA/SEMINARS/WORKSHOPS/COURSES/CONFERENCES

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
Symposium on Frontiers in Biology and Biotechnology	January 6-8, 1997; (at Vellore)	Dr. Anna Oomen, Organising Secretary of the Symposium, Department of Neurological Sciences, Christian Medical College, Vellore-632004.
International Symposium on AIDS and Hepatitis	January 9-12, 1997; (at New Delhi)	Dr. R.K. Tandon, Chairman of the Symposium, Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, New Delhi-110029.
XX All India Cell Biology Conference and Symposium on Recent Trends in Cell Biology	January 13-15, 1997; (at Mumbai)	Dr. R.A. Bhisey, Organising Secretary of the Conference, Cancer Research Institute, Mumbai-400012.
Symposia on (i) AIDS and Cancer Victims: Quality of Life, Psychosocial Interventions and Issues Related to Caregivers; and (ii) Divorce: A Grief Process	January 23-24, 1997; (at Manipal)	Dr. K.B. Kumar, Department of Psychiatry, Kasturba Hospital, Manipal-576119.
V Brain Storming Session in Molecular Immunology	February 21-23, 1997; (at Varanasi)	Dr. Ajit Sodhi, Coordinator of the Session, School of Biotechnology, Banaras Hindu University, Varanasi-221005.
International Conference on Developing Human Relations and Ethnic Understanding	February 26-28, 1997; (at Hardwar)	Dr. S.K. Srivastava, Organising Secretary of the Conference, Department of Psychology, Gurukul Kangri University, Hardwar-249404.

COUNCIL'S TRAINING PROGRAMMES FOR 1997-98

Leprosy

At the Central JALMA Institute for Leprosy, Agra:

- Training Course on National Leprosy Eradication Programme for Medical Officers (February 24-March 7 and September 15-26, 1997).

Virology

At the National Institute of Virology, Pune:

- Diploma in Medical Virology (July 1997-May 1998).

Reproductive Biology

At the Institute for Research in Reproduction, Mumbai:

- Training Course on Research Methods in Clinical Trials of Newer Contraceptives (April 14-25, 1997).
- Workshop on Genotoxicity (August 28-29, 1997).
- Workshop on Basic Molecular Biology for Clinicians (December 2-11, 1997).

Endocrinology

At the National Institute of Nutrition, Hyderabad:

- Annual Certificate Course on Endocrinological Techniques and their Applications (August 1-September 15, 1997).

Nutrition

At the National Institute of Nutrition, Hyderabad:

- M.Sc. in Applied Nutrition (June 1, 1997-February 28, 1998).
- Postgraduate Certificate Course in Nutrition (December 1, 1997-February 28, 1998).

Laboratory Animal Technology

At the National Centre for Laboratory Animal Science, National Institute of Nutrition, Hyderabad:

- Training Course for Laboratory Animal Technicians (June 16-July 31, 1997).
- Training Course for Laboratory Animal Supervisors (September 1-November 29, 1997).

Occupational Health

At the National Institute of Occupational Health, Ahmedabad:

- Orientation Course on Occupational Health for Industrial Medical Officers (September 30-October 11, 1997).
- Training Course on Environmental Hygiene Practice (November 10-14, 1997).

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