The observing team at the Indian Institute of Astrophysics consists of M. Appakutty, Pavan Chakraborty, G. Ganeshan, Alok Gupta, K. Jayakumar, V. Moorthy, S. Perumal and G. Selvakumar at the 2.34 m telescope. The spectra at the 102 cm telescope were obtained by Pavan Chakraborty and B. S. Shylaja of the Jawaharlal Nehru Planetarium. The author is responsible for the overall coordination of the project.

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Infectious diseases in a changing world*

V. Ramalingaswami

I present in this article a perspective on infectious diseases – newly-emerging diseases, resurgent diseases and simmering diseases that have a proclivity to break out in epidemic form from time to time, and view them in the context of rapidly changing life conditions in India and elsewhere. We live in truly remarkable times.

India and infectious diseases

India's health history is a mixed one, of successes and failures, and on the whole the balance of evidence suggests that India could have done far better in the health field than she did. There have been, of course, many successes and these have largely been on the infectious diseases front. But India's *problem is sustainability of those successes and overcoming the inertia and complacency following initial successes.* Once conquered diseases had lulled the country into dangerous complacency. DDT and chloroquine, ureastibamine and pentavalent antimony, multidrug treatment of tuberculosis and leprosy, diethylcarbamazine (DEC) against filariasis and now ivermectin, penicillin, streptomycin and the whole array of later-day antibiotics had enabled much progress to be made in the control of infectious diseases. Predictions that infectious diseases would soon be a thing of the past were made in the fifties and sixties of this century; a euphoria of the possible conquest of Tropical Diseases pervaded. Vaccination against childhood diseases in the form of the Expanded Programme of Immunization (EPI) is now increasing child survival enhancing optimism. All this had led to decline of mortality in the earlier age groups, increased longevity and the demographic transition (Figure 1).

And yet, the infectious diseases front is *a restless tide, rapidly changing and extremely worrisome*, unless society foresees the dangers and takes preparatory action. The fact is that infectious diseases continue to be leading causes of mortality in the world as a whole and in developing countries in particular and will be so well into the 21st century (Figure 2). We are in the midst of a rapidly-changing scene with regard to infectious diseases which consists of a mixture of newly emerging

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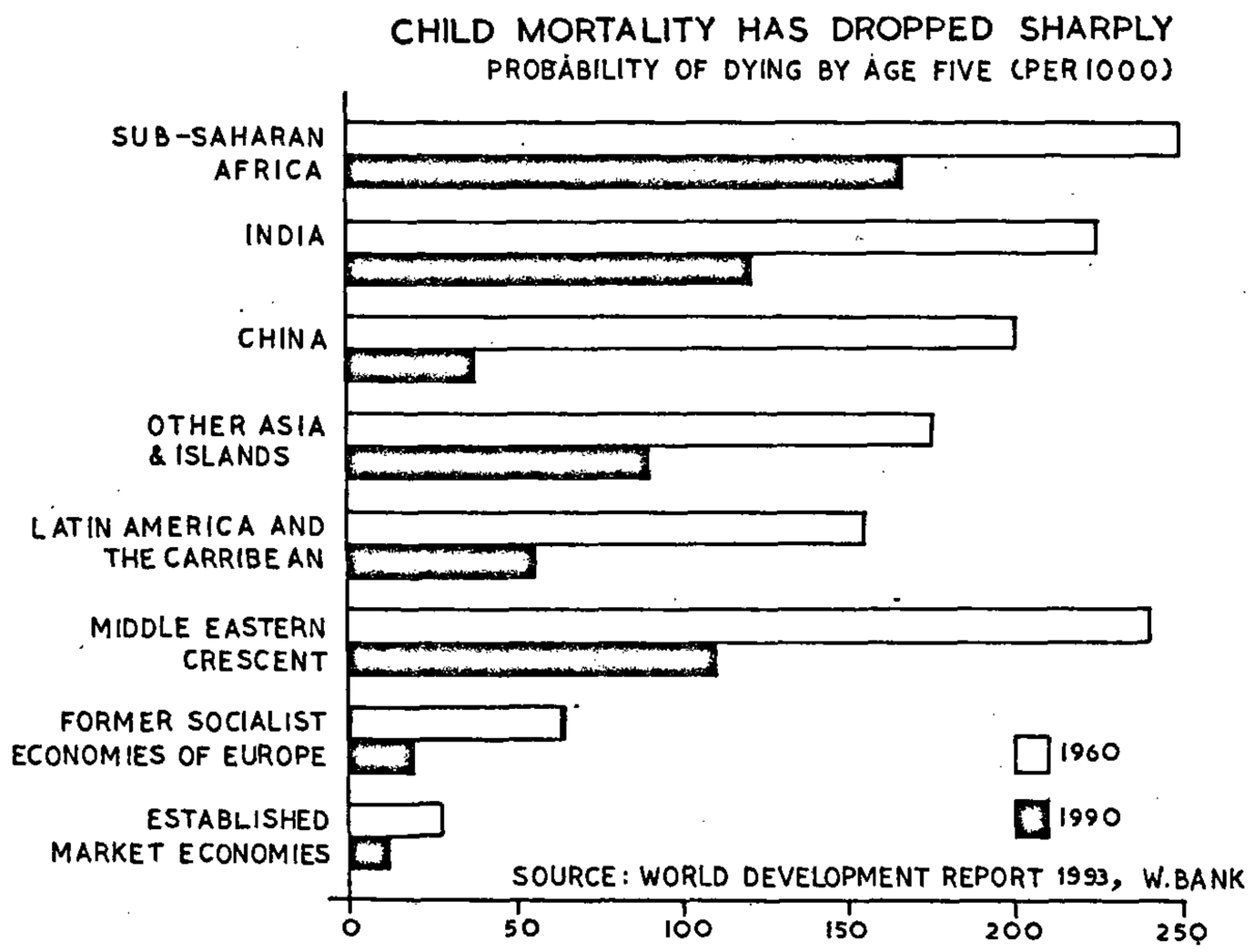

Figure 1. Sharp decline in child mortality rate.

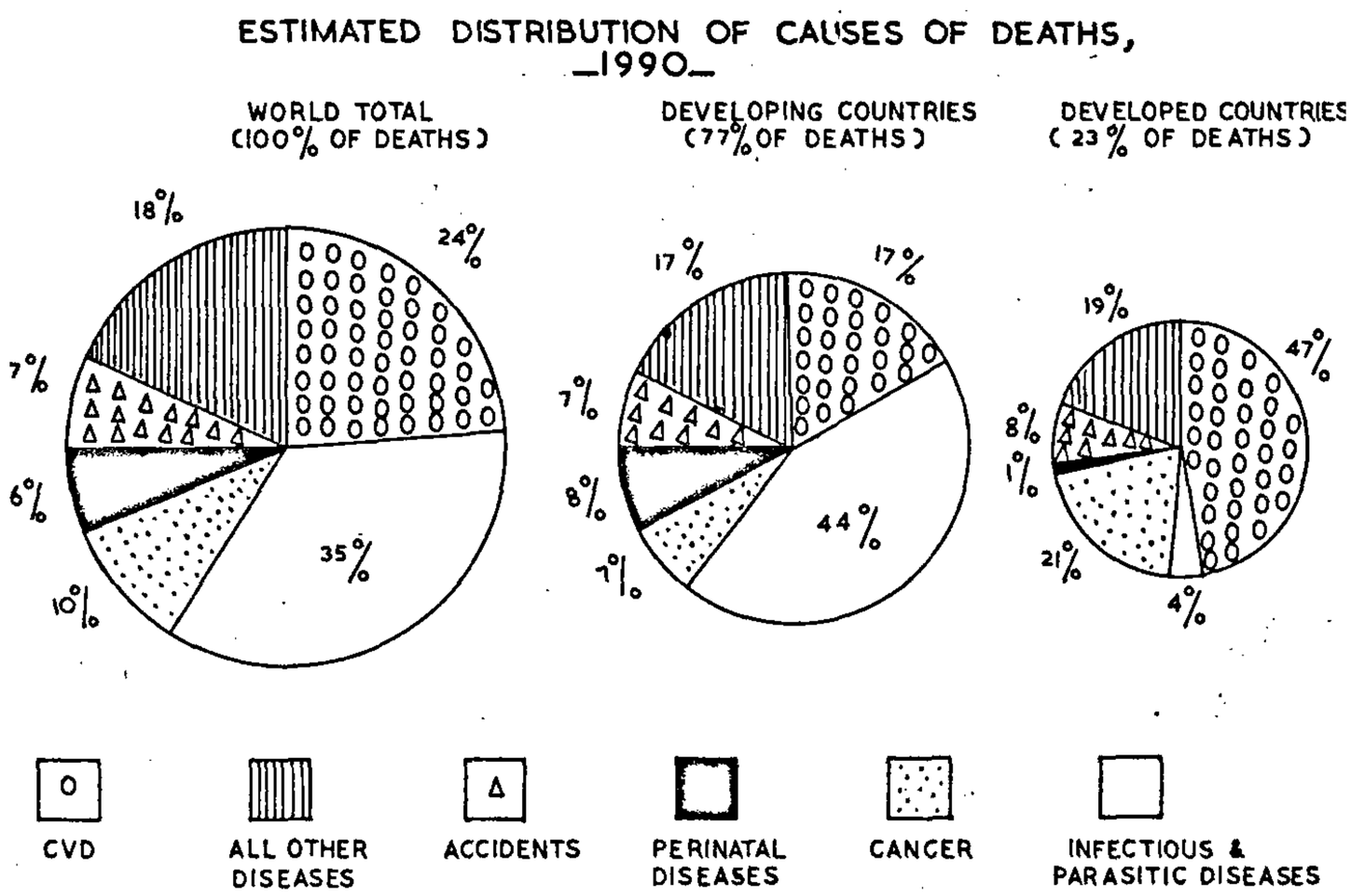

Figure 2. Estimated distribution of causes of death, 1990.

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healthy behaviour and public education; (ii) prevention through condom use; (iii) innovative protective devices that allow women to protect themselves; and (iv) vigorous campaigns for treating and preventing ulcerative genital disease. These sound like low technologies against an insuperable enemy and yet, if properly applied, they can yield significant results. Behavioural change is the AIDS virus' Achilles heel[5]; HIVs have a weak spot in that their range of transmission options is limited – sexual intercourse, blood routes and birth to an infected mother. The list stops there[5].

For vaccine development in which India has made no significant investment, there is the widening antigenic variability in surface antigens and genetic sequences of isolates from different parts of the world[6] – the HIV 1 B subtype in the industrialized countries; A, C and D in Africa; C in India and E in Thailand – provoking divergent immune responses and giving vaccine strategists a splitting headache! It stands to reason that vaccines in such situations have to be derived from the same Clades as are locally prevalent. India has no choice but to work on its own Clades and develop a vaccine on the basis of local strains.

Levy[7] suggests that for developing new drugs and vaccines, the large virus reservoirs of infected cells and tissues are more important than the free virus itself which is currently the target of intervention. He suggests that in future efforts, infected cells and cell-mediated immunity (CMI) should receive greater attention. What is needed is anti-HIV cellular immunity with memory in the infected host. Successful immunization has probably never prevented any viral infection in the early stages[7]. Whether it is treatment or prevention, approaches that kill the virus-infected cell should be encouraged. Vaccines together with selected cytokines which enhance CMI are the need.

Tuberculosis, a national emergency

The tragic tale of India not deriving maximum benefit out of its own discoveries made at the Tuberculosis Research Centre, Madras, with respect to multi-drug therapy against tuberculosis and in spite of a fine National Plan of Action for the Control of Tuberculosis extant for nearly three decades is well known. *Tuberculosis is still winnable just as HIV is preventable*. How I wish our efforts in India are geared to these realities! Six-month treatment with multi-drug therapy including Rifampicin under supervision was virtually permanently curative if the treatment was taken systematically over the required period of time[8]. Relapse rates were negligible. Case management packages with multi-drug therapy, passive case finding with bacteriological examination, programme management and directly observed treatment (DOT) can lead to a virtual cessation of transmission of TB infection in the general population, even under adverse conditions[9].

Unfortunately, this optimistic scenario has changed with the arrival and spread of HIV[8]. Multi-drug resistance, which is a bye-product of AIDS and which was not significant before, is now gradually assuming serious proportions in India. New drugs and new vaccines are on the horizon but time is of the essence and much more can be done even with existing technologies than is being done today. Not only must chemotherapy be ensured but also behavioural barriers must be broken. Sequencing the genome of *M. tuberculosis* is crucial for future advance and of course the policy of BCG vaccination at birth as a part of the EPI must continue even though BCG has had little epidemiological impact on TB incidence. Since there is evidence that it does prevent serious and often fatal forms of TB in young children, its use in the newborn is still vital. What is needed is a vaccine capable of protecting already infected persons from developing active disease. The variables in the TB eco-system explain the controversial results observed with community trials of BCG vaccine in different countries. *China's large-scale success in TB control shows that even now it is possible to control the disease effectively through case detection and treatment.*

The once conquered kala-azar

Once nearly eliminated in India in the sixties as a spin-off from anti-malaria operations, kala-azar has re-emerged in the last two decades; it is persisting and spreading geographically. The fires of kala-azar are still burning. An official paper from the Government of the State of Bihar gives a figure of 75,523 cases of kala-azar and 1,417 deaths from the disease in 1992 alone[10]. How distressing! and yet even with the existing technologies and state of knowledge, the disease is controllable to a significant extent. The vector of kala-azar, the sand fly, is still believed to be susceptible to DDT to a large extent. It is limited in its dispersal, largely endophilic and intra-domiciliary and so with correct application of residual DDT spray, taking into account vector behaviour and transmission seasons, effective vector control should be possible. With early detection of kala-azar through the use of the direct agglutination test (DAT) and the more recently introduced molecular methods[11], and institution of prompt and complete treatment with pentavalent antimonials, effective case control should be possible. The use of pyrethrum impregnated bed-nets is an additional vector control intervention. *Again, time is of the essence.* Although kala-azar transmission is a complex ecological phenomenon, many facets of which are still poorly understood, nevertheless, before the echoes of parasite and vector resistance become louder and shriller, kala-azar can be

controlled and its prevalence reduced by three-quarters by 2000 AD.

Lymphatic filariasis spreading to rural area

Lymphatic filariasis is another disease that is either stagnant or spreading, largely due to ecological changes and human migration. It is a disease that causes much disability, suffering and social discrimination, out of proportion to the relatively low mortality that it causes, and yet it is one of the most prevalent of conditions. In India alone 381 million people are exposed to the risk of infection, 25 million persons are microfilaria-carriers and 19 million suffer from chronic filarial disease[12], and if more sensitive antigen detection methods were available, the infection rates would be much higher. 751 million persons around the globle live in endemic areas. Filariasis in rural areas is emerging as a major vector-borne disease making inroads into newer areas[13]. Recent studies in India indicate that the acute inflammatory manifestations of lymphatic filariasis are more common than was believed formerly, almost 10–20% of the infected showing these manifestations leading to loss of working and productive time and considerable suffering[14]. The chronic manifestations, in the form of hydroceles, lymphoedema and the much-feared elephantiasis, chyluria and the pulmonary eosinophilic syndrome, all these affect nearly 30 million persons in India. Strategies for control must be based on location-specific factors and although it may be difficult to eliminate lymphatic filariasis altogether in the near term, a variety of technologies that are available (Figure 3) and the experience behind them provide hopeful signs for better control of filariasis. The approaches consist of vector control, reducing vector/human contact and chemotherapy and in each of these areas, there have been significant developments. Environmental management, including the use of biological methods for the control of mosquito vectors, in particular the use of *B. spheri cus*, have proved to be effective in the Indian experience and could be used more extensively in selected areas. In the area of chemotherapy, ivermectin in the dose of 400 µg/kg can suppress microfilarial production for almost a year and similarly a single dose of 6 mg/kg of DEC can be equally effective and a combination of the two, a very low dose of ivermectin 20 µg/kg with 6 mg/kg of DEC provide the best results[15]. We have now entered the era of a single dose given once in a year to populations can bring about a substantial mass effect in the control of a tropical disease. Excellent results have been obtained by the addition of very small quantities of DEC to common salt both as a therapeutic and prophylactic method when used for over six months[15]. There has been Indian experience on this as well as large scale Chinese experience. With the decision already made and implementation in progress for the universal iodization of salt for the control of iodine deficiency disorders and with the developments now taking place for the addition of iron to common salt for the control of nutritional anaemia in India, DEC is another entrant into the salt fortification programmes and it is necessary to work out how best this could be added to salt in specific areas when iodine and/or iron deficiency problems also exist side by side.

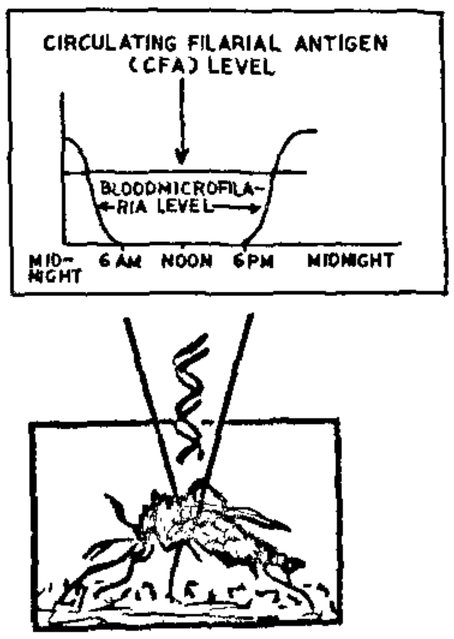

Figure 3. DNA probes – Sensitivity and specificity detect parasites in the mosquito vector and can be used to monitor effectiveness of *programmes to control transmission* (Source: WHO, TDR).

DEC and ivermectin given as a single annual dose, medicated salt, biological control methods, integrated vector control – all these offer a scenario of promise for the control of lymphatic filariasis but the essential problem still remains, – of improvement of the management system, logistics, community participation, monitoring and evaluation, which are so critical for the control of many a tropical disease.

Cholera conundrums

India had long been the home of cholera but the disease had lost much of its fury in recent times, largely because of the use of oral rehydration therapy. This does not mean that the cholera front is static and not a cause of worry. A new strain of *Vibrio cholerae*, 0139 Bengal, is now replacing the classical 01 strain in several parts of India, first detected in South India in 1992, setting the stage for the 8th pandemic of cholera[16–18]. There is a battle of the two organisms currently raging in the environment for supremacy. 0139 seems a harder bug and more likely to survive in the environment but the low asymptomatic infection rate with this organism gives a selective advantage to 01. 0139 produces identical clinical expression of disease as 01 with severe dehydration and hyponatraemia but, fortunately, susceptible to tetracycline and ampicillin. It seems to be losing ground to 01 but the future alone can tell the final outcome. We should be quite prepared that the events on this front, especially with the vagaries of the monsoon, may be

unpredictable. Immunity to *V. cholerae* 01 cannot protect against *V. cholerae* 0139. We must constantly monitor areas with poor sanitation and take advance action. Chlorination of water still works. Boiling of water is, of course, effective. A fresh dimension added to the ecology of cholera infection is that outbreaks can be predicted today through satellite images for phytoplankton blooms. Phytoplankton serves as food for zooplankton and zooplankton harbours cholera vibrio. For a whole century, the whole of Latin America was free of cholera, until 1991 when an epidemic started with El Nino, an occasional ocean current that brings unusually warm waters to the Peruvian shore, thus creating conditions right for planktons to bloom. The increase in coastal blooms is a direct consequence of human activities, some local and some impacting on global climatic conditions[19,20]. There is an urgent need for an effective orally administered vaccine. There is encouraging news on this front from three Indian laboratories – the Institute of Microbial Technology, the Institute of Chemical Biology and the Central Drug Research Institute.

A new paradigm of infectious diseases

My thesis is that *India is in a fragile situation with regard to infectious diseases. The scenario is one of new diseases, e.g. HIV/AIDS, re-emerging diseases, e.g. malaria, kala-azar and plague and diseases that are simmering and that have a high probability of breaking out in epidemic form given favourable ecological conditions, e.g. tuberculosis against a background of spreading HIV infection, cholera, and dengue haemorrhagic fever. A new paradigm of infectious diseases has to be addressed comprising not only of parasites, vectors, bacteria and viruses, but of a whole host of factors connected with lifestyles, urbanization, increasing speed of travel, tourism and trucking, behavioural factors, wars, and local conflicts, ecological disasters and massive migration of human populations.* In the midst of such rapidly-evolving scenes, there is a significant impact on public health, especially on infectious diseases.

Even so, the infectious diseases situation can be substantially improved by more effective application of existing technologies, control policies geared to epidemiological realities, improved logistics, reliable reporting systems, monitoring and availability of first-line drugs and education and community participation. In public health, time is of the essence especially in infectious diseases so as not to allow time and opportunities for organisms and vectors to develop resistance. An agenda must be drawn up where more effective interventions on the basis of existing knowledge can be made in respect of many infectious diseases, be it tuberculosis, kala-azar, malaria or filariasis. The example of leprosy should be studied to identify the success factors behind a programme that came to life so very recently. At the same time, the need for new knowledge is paramount.

Basic sciences for development

While existing technologies must be applied in a more effective way, the new and modern techniques in biology must make their way into medicine and public health everywhere including developing countries and speedily[21]. The example of hepatitis vaccine may be cited.

Hepatitis B vaccine

Hepatitis B vaccine is now available which can prevent chronic hepatitis, cirrhosis and liver cancer, a major problem of developing countries. It is a matter of regret, however, that India is still on an uncertain course with regard to the control of hepatitis B. The best estimate on the basis of studies made so far indicates that 2–5% of the population are carriers of hepatitis B virus; thus there are approximately 34 million HBV carriers in India constituting 10% of the entire HBV carrier pool in the world[22]. India has the second highest number of HBV carriers after China[22]. It is quite clear from the evidence obtained so far that routine infant immunization through the Expanded Programme of Immunization is a favourable interventional form from an economic point of view as well and this is already a National Policy in many developing countries with low endemicity[23]. India can no longer sweep the Hepatitis B virus problem under the carpet. It is well known that the hepatitis B vaccine is the first vaccine against cancer and hepatitis B is second only to tobacco as a carcinogen. The cost factor is no doubt a problem, but is coming down and a beginning can be made in smaller, more affluent states in India.

Early diagnosis of infectious diseases and molecular epidemiology through nucleic acid-based methods are critical for the fight against infectious diseases (Figure 3) dominant in developing countries today, for example, HIV (Human Immunodeficiency Virus), HBV (Hepatitis B Virus), HCV (Hepatitis C Virus) and HPV (Human Papilloma Virus) infections, sexually-transmitted diseases, mycobacterial infections and drug resistance of microbial pathogens. The whole field of transforming findings in basic science to meaningful application in resolving health problems affecting vast numbers of people in developing countries needs urgent attention. These challenging areas are candidates for the successful application of basic science in the near

Table 1. Emerging diseases: Epidemic outbreak–cholera, plague and ebola

Epidemic outbreak	First suspected case found and informal report issued	Government or local authority reported to WHO	WHO intervention international team started and ended	Current status
Cholera Peru and later in other Latin American countries	January 1991	February 5, 1991	February 7, 1991	Low level of endemic
Cholera, Rwandan refugee camps in Zaire (Goma)	July 20, 1994	July 20, 1994	July 25, 1994 August 12, 1994	No report of endemic
Plague in India (Maharashtra)	August 26, 1994	September 28, 1994	October 13, 1994 October 26, 1994	No report of endemic
Plague in India (Surat)	September 22, 1994	September 28, 1994	October 13, 1994 October 26, 1994	No report of endemic
Ebola haemorrhagic fever in Zaire (Kikwit)	January 1995	May 6, 1995	May 9, 1995 –	Low level of transmission continues

future. They show how thin the dividing line is between basic science and applied science. As Sir Hermann Bondi said, 'Basic science is the well-spring of the modern economy'. Basic discovery and application must be moved closer together. One way, as the British Labour Party suggests, is to create overlapping networks in which scientists and industrialists meet and exchange ideas from time to time. Molecular biology of which the Indian Institute of Science (IISc) is a pioneer in this country, through biotechnology, has great power to overcome disease and promote health and thus make a direct contribution to society in the developing world.

Infectious diseases, environment and ecology

An ever-changing tide of infectious diseases persists in rich and poor countries, particularly the latter[24,25]. Emerging and re-emerging diseases are an index of large-scale environmental change. The rise of HIV/AIDS throughout the world, especially serious in the Third World, cholera in Peru and Equador related to blue-green algal blooms, the emergence of *V. cholerae* 0139 in South Asia, the re-emergence of malaria, and kala-azar and plague in India, the accentuation of tuberculosis in many developing countries and the recent spread of viral haemorrhagic fevers in the wake of deforestation and extension of agricultural irrigation, the recent increases in antibiotic resistance of a variety of microbial pathogens are indications of microbial adaptation and resistance and exploitation of new ecological niches[24] (Table 1). Many health phenomena today reflect population pressure, human mobility, local climatic change, invasion of Nature's fringes, all impinging upon the prevalence, distribution and spread of infectious diseases[25]. The resurgence of plague in India in 1994, after three decades of absence from the country, is probably related to environmental disturbances caused by a major earthquake in one area and heavy monsoon rains in another[26]. Disruption and destruction of the world's natural life support systems constitute the greatest threats to improved human health[24]. Ecological infringement, human mobility and human social change are potent forces for new infectious disease to emerge or resurge.

Final comments – the art of the possible in molecular genetics

In concluding I would like to allow myself the luxury of a vision of *the art of the possible* in the exciting field of molecular genetics in general. Can humanity cope with the knowledge that is flowing out of the DNA revolution? The Human Genome Project and the Human Genome Diversity Project, in which the IISc is taking an active part, are now racing to write down the anatomy of the entire DNA molecule[27]. The Nuffield Council on Bio-ethics in the UK said two weeks ago that it was morally acceptable to use organs from genetically engineered pigs for transplantation into humans. All the 4000 diseases caused by a single gene mutation would be traced to precise location on the 23 chromosomes. Polygenic syndromes would also be mapped. Human behaviour associations with genes would be greatly illuminated. Genes may be inserted to permanently cure genetic disorders, to eradicate AIDS or to increase human intelligence. Treatment of disease and its prevention will be the greatest benefit to mankind out of molecular genetics – diseases that occur in large numbers, that have remained obscure, that are difficult to diagnose and impossible to treat. I am delighted that Japanese encephalitis, mycobacterial diseases and microbial resistance are receiving increasing focus at IISc

from a molecular perspective. The ethical implications of the new genetic knowledge are complex and yet humankind must face and resolve them. *It will be necessary to ensure total genetic privacy and to outlaw all forms of genetic discrimination.*

Molecular genetics can be a healing force that humankind, through prediction, can offer parents to adopt the most rational approaches towards their offsprings, threatened with disabilities. It can provide detailed molecular information that will lead to a precise design of new drugs and of course it can lead to gene therapy. There is a fear that molecular genetics may reintroduce 'eugenics' behind the mask of health care. Mankind has to be alert to ensure that unethical use of genetic knowledge does not take place. An educated public is the surest means of ensuring that genetics does not become dangerously politicized. A pessimistic thought might enter human minds that if it is all in the genes, why bother to improve social conditions, education, health and welfare? Gene technologies far from being predestined and cursed, should help people in breaking out of genetic stranglehold and achieve a balance between gene power and environmental modification of that power in order to produce a balance of forces that will be conducive to the development of a wholesome fit between environment and the genome[27]. This is the time to prepare the human ground, society and civilization, to use the new genetic knowledge wisely, humanely, equitably, with social justice, enhancing autonomy and human dignity. Through gene technologies, may we play the role fully of *Responsible Ancestors*.

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