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Modern Biology and Medical Advance

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The Indian National Science Academy has taken some initiatives in the past few years for the promotion of molecular biology and its offshoots—recombinant DNA, and hybridoma technologies. I believe that these developments in modern biology hold great promise for the improvement of health conditions throughout the world, especially of the problems of communicable diseases and excessive population growth that continue to bedevil the developing countries. Indeed, the possible benefits are likely to extend far beyond medicine and health into wider fields such as industrial chemistry, pharmaceutical industry, agriculture, energy production and even mining. They have profound implications for the future of man.

Fundamental biology has made greater strides during the past quarter of a century. Our knowledge of cellular and molecular functioning is now quite profound. Ruthless reductionism, the essential pathway of science, has paid handsome dividends. The newer techniques of molecular biology, cell-biology, genetics and immunology have played a key role. Concentration on simplest models such as viruses, bacteria and cells isolated from complex organs was of strategic importance. Cf particular significance was the ability to separate pure populations of single species of molecules and even cells from complex and largely uninterpretable mixtures. As a result, we now have deeper insights into the structure and organisation of the constituents of life processes, of the evolution of form and function in living organisms, of differentiation of cells and of genetic polymorphism. Perhaps within this decade, we will see a much more elaborate and sophisticated picture of the chemistry of life.

The breathtaking events in molecular biology in the past few years have come sooner than anticipated. Hybridoma technology is no more than five years old, and the recombinant DNA technology is no more than seven years old. It is now obvious that it is possible to reorder genetic material at will, and to grow unlimited copies of genes of humans and animals in bacteria. Bacteria can be manipulated to synthesise biological materials that evolution has assigned exclusively to be made by the human species. We can now say that modern biology will exert a considerable influence on the health and well-being of mankind in the years to come (Stoker 1980, Ramalingaswami 1980b).

The first intellectual bonuses—the human growth hormone, insulin and interferon

The first intellectual bonuses came when it became obvious that scarcely available substances such as human insulin and human growth hormone could be made by bacteria through the gene cloning techniques apparently in unlimited quantities. Human insulin and human growth hormone have already been made in the laboratory by the recombinant DNA technology. So also, human interferon, the glycoprotein which seems to be the key immuno-regulatory signal for the Natural Killer (NK) cell activity (Bloom 1980). The growth hormone gene was inserted into *Esch. coli* and the bacteria were made to synthesise the hormone. This recombinant-derived human growth hormone was able to produce the same amount of growth in growth hormone-deprived animals as natural growth hormone isolated from human pituitaries. This should provide almost limitless supplies of this hormone for treating growth failure in children and perhaps also for improving the healing of wounds and fractures.

The human insulin produced by genetic engineering compares very favourably with porcine insulin that is being used in clinical practice today when tested in healthy human subjects. Insulin-producing cells have been transferred successfully from rats to mice in whom diabetes has been produced experimentally and the diabetic mice have been restored to normal.

Interferon is being hailed as an extraordinarily potent substance which protects against viruses and slows down growth of cells thus offering a tool for the treatment of cancer as well. It is generally regarded as the wonder drug of tomorrow. Up until now this unique protein was so scarce that it cost 150 US dollars for a single dose and 30,000 US dollars for a full course of treatment. It was being produced by the traditional processes using human cell cultures. The possibility of genetically engineered bacteria producing interferon in unlimited quantities is now established. Apparently the low yields have now been improved considerably. There is a spectrum of interferon proteins and a number of different genes code for them. A great deal of very careful clinical experimentation to evaluate the usefulness of interferon remains to be done. The world is waiting for the interferon story to unfold itself.

Genes and minigenes

Recent work has shown that the genes of animal viruses, and of animals including man, occur in pieces spread out along the DNA. There is now a better understanding of how these genes occurring in different places are expressed. Each gene fragment, designated by Dr Gilbert, the 1980 Nobel Prize winner, as minigene probably codes for a functional part of a protein. Gene fragments probably code for specialised cell products like globin, insulin and antibodies. Gene regulation is now becoming more clearly understandable.

Monoclonal antibodies

Equally spectacular are the possibilities in the field of monoclonal antibodies produced by hybridoma technology. They have a number of uses in the diagnosis, epidemiological study, treatment and prevention of a wide variety of viral, parasitic and bacterial diseases. They would enhance organ transplantation capabilities by world-wide standardisation of tissue typing (Milstein 1980). Monoclonal antibodies would revolutionise the traditional methods of serological diagnosis and serum treatment. They would help in characterising the antigenic complexity of cell surfaces and detect differentiating antigens in a number of species.

Monoclonal antibody is a well-defined chemical reagent that can be reproduced at will, in contrast to a conventional antiserum which is a variable mixture of reagents and can never be reproduced, once the original supply has been exhausted (Milstein 1980). These antibodies can identify new surface molecules and at the same time distinguish amongst cell populations. The monoclonal approach to characterising differentiation antigens makes it possible to find out the stage at which an antigen is expressed. The Cascade purification method is being applied to characterise the antigenic complexity of cell surfaces (Milstein 1980).

Monoclonal antibodies are replacing conventional anti-sera in standard kits for radioimmunoassay procedures. An extraordinarily wide range of applications is envisaged including the study of receptors for hormones and neurotransmitter substances. A very major impact is likely to be exerted by the monoclonal antibodies being used as passive immunising agents for protecting against a variety of infections. They would pave the way for the development of improved vaccines. They have already proved to be of immense value in the field of malaria and have been shown to provide protection in animals against lethal challenges with malarial parasites.

Because of their extreme specificity, the monoclonal antibodies can be used to identify and purify molecules of interest in almost any field of biology (Yelton & Scharff 1980). They allow one to be able to differentiate between strains of viruses (Gerhard et al. 1978, Koprowski & Witker 1980). Hybridoma technology is a cell fusion technology which provides continuous antibody forming celllines. Hybridoma cell is produced as a result of fusing an antibody producing cell with a tumour cell. This hybridoma cell grows and divides endlessly and all the progeny from the original hybridoma cell secrete the same pure antibody (Cape 1979). They are extremely uniform and reproducible. They have been made up to now by the mouse myeloma cells but they have just recently been reported to have been made from human cells also. These antibodies can attach themselves to important sites on cell surfaces thus acting as guided missiles. The antibodies selectively attach themselves to certain cells and can deliver a dose of destructive material to these cells. The material can be a powerful anti-cancer drug or a toxin and the rest of the body tissues and cells are not affected.

The challenge of tropical communicable diseases

It is in the control of some of the intractable tropical communicable diseases that I believe lies the real challenge to molecular biology. Confronted as we are with a situation in which: a) *Plasmodium falciparum*, the most dangerous form of malarial parasite, is resistant to the most widely used antimalarial—chloroquine; b) several species of mosquitoes that transmit malaria are resistant to the commonly used insecticides on which we are dependent today for mass use; c) for mass control of leprosy, we depend upon only one drug 'dapsone' against which the leprosy bacillus is showing increasing evidence of resistance; and d) we have only one effective microfilaricidal compound, thio-carbamazine to fight filariasis—these reflect the technological despair which surrounds the whole scene of control of tropical communicable diseases especially malaria, filariasis and leprosy. It is through a better understanding of the biology of these parasites and microbes that we can hope to develop new strategies and new approaches for their control. We have to understand the tricks that the parasites play. How do they avoid host defences? How do they acquire drug resistance? Modern biology should enable us to attack the

vulnerable sites in the life cycle of these parasites. The technologies that I have described should enable us to prepare pure parasite antigenic material. Parasite genes coding for important antigens could be identified and transferred to harmless bacteria, getting the bacteria to make the antigenic material which can then be used for diagnostic as well as prophylactic purposes. Modern biology should enable us to block the attachment of parasites to specific host cell membrane receptors making it difficult for them to survive and multiply. A drug may be linked to a molecular carrier preferentially homing to vulnerable sites in the parasite. Drug-liposome and drug-antibody complexity offers interesting possibilities.

Gene treatment

There are possibilities in the future of being able to correct at least some genetic defects through the techniques of molecular cloning. Single gene errors may be correctable. Sickle cell anaemia is due to a single variation in a group of genes involved in the synthesis of haemoglobin. Gene treatment is in the realm of possibility of molecular biology, but there is a long way to go from the present position to the repair of genetic defects in intact human beings. Single genes have already been injected into defective living cells in culture and have cured those cells of genetic defects.

Modern biology in agriculture and industry

Genetic engineering might make it possible to increase the efficiency of photosynthesis and to improve nitrogen fixation. It may also be possible to identify genes that make plants more tolerant of salinethan others. The importance of this technology is obvious considering the problem of increasing salinity of our soils following irrigation. The disposal of agricultural and industrial wastes could be accomplished with useful by-products by the use of bio-technology. Fermentation industry can benefit enormously by the gene splicing technology for large scale production of amino acids, nucleotides, organic acids, etc. It is possible to stitch into the DNA of industrial micro-organisms the human genes to render the microbes capable of producing vast quantities of widely needed substances (Cape 1979).

Chemical transformations in industry are normally performed at high temperatures and high pressures needing high inputs of energy. The gene technologies will be able to accomplish the same thing with low energy inputs because the work can be done at room temperature and at atmospheric pressure. The problem of wastes will probably be minimised in the biological production systems.

Brain chemistry

There has been a quantum jump in our understanding of brain chemistry in recent years. Until 10 years or so ago we were 'limping along' on a few classical neuro-transmitters, and electro-physiology was the main tool for studying brain function. No doubt much has been learnt by these techniques. Today, there are literally dozens of neuro-transmitters, neuro-peptides and neuro-hormones discovered which constitute the biochemical circuitry of the brain. There are expectations that the endorphins and the encephalins may pave the way for a possible solution to intractable pain and drug addiction. There are hopes of a better understanding of human feelings and human behaviour, of learning and memory, of sleep and of various levels of consciousness. The brain's medicine chest has been at least partially opened and this has unfolded the brain's incredible chemical repertoire. Simultaneously, there are major advances

taking place in psychotropic drug development. The screening of potential psychotropic drugs has moved from the laborious animal testing, the old black box approach, to the world of molecular biology. The assay of drugs for their effects on behaviour is done on isolated brain cells. The area is undoubtedly full of promise for an understanding of how the brain functions, but in terms of practical benefits to cater to the needs of 'choose your mood' society, one should not expect results around the corner (Gurin 1980).

Hepatitis B vaccine and liver cancer

I cannot let this occasion pass without referring to the developments leading to hepatitis B vaccine. The vaccine is itself the outcome of basic research in biology and clinical medicine. In October last year, a report by Dr Szmuness and his colleagues indicating the remarkable success of a carefully controlled hepatitis B vaccine trial in a high risk population of homosexuals in the United States has been regarded as a milestone in the annals of preventive medicine (Zuckerman 1980). Hepatitis B is of great public health importance in our country as well as in many developing countries. It has been estimated that there are as many as 200 million people who carry the hepatitis B virus in their blood, known as chronic carriers. The vaccine contains 22 nm hepatitis B surface antigen particles which are derived from the plasma of healthy carriers and inactivated with formaldehyde. Infection with this virus can lead to a form of chronic liver disease including cirrhosis and there is also an association with primary liver cancer. The work done by Professor N C Nayak in our country has shown the close association between primary carcinoma of the liver and the presence of hepatitis B surface antigen in nearly 100 % of all cases of primary liver cancer both in our country and in Africa. The vaccine against hepatitis B can be of great value in protecting persons who constitute high risk groups against this form of hepatitis. These are persons who receive multiple blood transfusions and patients and staff working in the kidney transplantation and haemodialysis units.

There is considerable evidence to suggest that infection with hepatitis B virus is an important precursor to the development of liver cancer. There is strong geographic correlation between hepatitis B infection and liver cancer and there is also some evidence to indicate that a substantially large proportion of mothers of patients with liver cancer are chronic carriers of the hepatitis B virus. The link between the hepatitis B virus infection and liver cancer has received further support from the reports published by four groups of independent workers which show that the DNA of the hepatitis B virus is integrated into the genome liver cancer cells (Journal of Virology, *33*, 795, 1980 and Nature, *286*, pp. 531, 533 & 535, 1980). Although this does not prove that the virus is responsible for producing the cancer, it is once again an additional piece of evidence to support the connection between the two. If from all the evidence that is presented so far, hepatitis B infection is a prerequisite for the development of liver cancer subsequently, then the elimination of that infection through hepatitis B vaccine should also eliminate the development of liver cancer. Already, the 1980 Nobel Laureate Dr Gilbert of Harvard University and others working in Edinburgh and Heidelberg have reported that they have been able to insert hepatitis viral genes into bacteria and both hepatitis B surface antigen and a protein from the virus core are being produced by the bacteria.

Conclusion

The new technologies will take time to move from laboratory scale to large scale produc-

tion. But from the kind of rush that one sees in this area, it can be expected that the transition from experimental to clinical level application will take place sooner than later. This is all to the good but in all this, what guarantee is there that these products for the health of man will be accessible to those in greatest need at prices that they can afford? The history of science and technology repeats itself—each major advance enhancing the dependence of developing countries upon the developed ones.

It is sometimes said that basic research and high technology are for developed countries and that appropriate technology will do for developing countries. While I am second to none in upholding the importance of appropriate technology for developing countries, no country, developed or developing, can do without basic research and no sustained development is possible without it (de Duve 1980). In this particular case, India has a unique opportunity to develop a solid programme of basic research in modern biology and a whole range of skills in molecular biology to resolve some of our health problems and to speed up overall development. Finally, the fast-moving events in molecular biology must be coupled with human wisdom in their application, if we are to reap the full benefits of this technology without paying a heavy price. The earlier concerns about the safety of gene splicing techniques have now somewhat receded to the background, but the question of careful use of the new and powerful products available in large quantities still remains. Their safety will have to be very carefully evaluated. A whole range of ethical issues will have to be faced. The question of gene therapy, for example, will raise a number of such issues. Ethical guidelines in such matters are much more difficult to develop than guidelines of safety (Dickson 1980).

The new Biology cannot remain isolated from social issues. As I said in my Annual Address last year the future lies in broadening the horizon of interplay of bio-medical and socio-medical research and in transdisciplinary synthesis of science and technology with society's needs and human values in a changing world (Ramalingaswami 1980a).

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