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THIRD P M S BLACKETT MEMORIAL LECTURE

Some Hopes and Fears in the Biosciences

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Mr President and Fellows

It may seem odd to you that a biologist, and a medical one at that, should have been chosen to commemorate Lord Blackett, one of our most distinguished physicists. The first two Blackett Memorial Lecturers were indeed distinguished physicists themselves. My colleagues felt, however, that a third physicist would set the precedent for all time, and would discourage something Blackett himself strove for, both here in India and Britain, namely a broad view of science and its application. My own small contact with Patrick Blackett was in connection with the expansion of molecular biology and its organization on an international basis, to which I shall be returning later.

But in appearing before the Academy, I should like to present one small credential, namely the fact that my research career began here in India. This was in 1944 when a group of Indian and British microbiologists were working together on the problem of typhus. Incidentally, since I am going to discuss some of the hazards arising from research, it is appropriate to mention that most of us caught typhus and we all survived.

In this lecture, I wish to review the future potentials of the research which is rapidly developing in the biological sciences, in particular relation to the obstacles which arise through new fears about possible It is a dangerous subject which could equally be discussed in the context of the physical sciences, in relation to energy, for example, or the physical environment.

Contributions from the Biosciences

I suppose the contributions from biology in the last 100 years which have had the largest potential effect throughout the world are the conquest of major infectious diseases, and more recently the green revolution which has led to major increases in crop yield.

Disappearance of infectious diseases as the major cause of death in many, though not all parts of the world, was partly due to improvements in sanitary engineering, and it has been argued that this, rather than biological research, was the main contribution. The argument, however, can be overemphasised. Some diseases, poliomyelitis for example, were made worse by improved sanitation, because infection was delayed until an older and more vulnerable age, and they were odly conquered as a result of direct biomedical research. In any case improved hygiene was itself based on the era of microbiology begun by Pasteur. The great advances continued in this century have in fact, been the consequence of research on mechanisms of transmission of infectious disease, much of it carried out here in India, on immunity mechanisms and preventive vaccination, and finally on the discovery of chemotherapy and the antibiotics. If it were not for these discoveries many of us would not be at this lecture, because we would have died in childhood.

The other great contribution, the green revolution, is particularly familiar to you here in India. Indeed the work of Indian plant geneticists in adapting the high yield varieties of rice and wheat to the local environment, and the resulting increase in crop yield is one of the great triumphs of your country. It is renowned throughout the world and a great example for the future. But modern plant breeding is based on the emergence of the science of genetics and without that branch of biological research the green revolution might never have happened.

These are only two of the contributions of biological science, but they have probably affected greater numbers of humans throughout the world, both in developed and developing countries, than any others. Indeed if I may be so bold, they have probably had more beneficial impact on the human race than any advance in the physical sciences. Like all discoveries, however, they have brought new problems in their wake, which now loom over us as threats for the future. The threats arise from the very benefits of the last decades, longer life, and lower mortality, leading to increasing and eventually aging populations, with incessant and unremitting demands.

In the short term the threats and challenges of overpopulation, and, the equivalent in the west, an overdemand by the same population, must be met not by new inventions and discoveries, but by improved management, development and application of knowledge which already exists. But in the long run the solutions, and in fact our salvation, be it in India or Britain will depend on new knowledge and new discoveries which will be made in coming years in the world of scientific research and technological development.

The Biosciences and the Future

Consider for a moment the problems which will be the particular concern of the biological sciences. First, there will still be the problem of food. Deliberate changes in amino acid content of cereals are being actively pursued. We shall also see an increasing concern with the problem of nitrogen fixation, because of the diminished reservoir of fertilizers, and the development of quite new types of organisms, even with semi-synthetic genotypes, for conversion of solar and other forms of energy into food. Biology will also have to face the threat of new pests which will inevitably develop along with the new varieties, and which have indeed already appeared amongst the high yield varieties of cereals currently in use. Pest control will also depend on the new genetic methods and new findings in cellular biochemistry, rather than the successful methods of the past, such as wide but empirical screening of possible pesticides. Then, since climate control is a long way off, there will be the demand for new types of plants which are drought resistant and can be used to populate some of the world's desert areas. Classical breeding methods will probably have to be reinforced by new types of genetic manipulation. For a start this needs the cultivation of isolated plant cells, protoplasts, from monocotyledons.

In medicine, in addition to malnutrition, and parasitic infections, the challenges which face us are the non-infectious diseases which have become the major cause of death and disability in many countries, namely heart disease and cancer. No one expects these to be conquered by application of current knowledge, and they await major advances in the understanding of the molecular mechanisms behind living processes.

There is finally the very controversial question of population control itself. I do not intend to enter this particular minefield in your country today, except to point out that research in reproductive physiology ought at least to provide a variety of new approaches to the solution of the problem.

These new challenges, of which the above are only a few examples, appear before us at a particularly interesting time in the development of biology. It is a time of enormous excitement because it coincides with the new confidence which has emerged from the first decades following biology's own revolution. This is loosely called molecular biology, but it involves a much wider change in outlook, particularly at the cellular level. The confidence, which now results, comes from a feeling that in the long run the problems of biology are soluble and not forever shrouded in mystery.

But coincidentally there is an increasing disquiet and fear about the consequences of science. A recent poll in several European countries on behalf of the European Economic Community showed that a majority in European countries are deeply concerned about the new science-based technologies, affecting living, traffic, drugs, etc. From our experiences in Britain concern is certainly not limited to nuclear reactors, atmospheric CO_2 or other aspects of the physical sciences. Population of the environment is a constant preoccupation, and so is the concern that science is not being properly used to benefit a sufficiently wide section of the human race. Of greatest significance however is the change in attitude since a similar survey two years previously, which indicated that time, there was no widespread mistrust of science.

A similar trend seems to be occurring in attitude in North America. Whether there is disquiet about science in other scientifically developed countries, such as India or the Soviet Union, I do not know and rather doubt. But I do believe that some of the worries and fears, and the altered attitudes to science, which are apparent in the west, are worth your own consideration, not least because they may be an obstacle to the solution of some of the global problems which I mentioned.

Let me therefore give you some examples of public disquiet in fields in biology with which I am familiar.

Dangerous Pathogens

Last year the World Health Organisation was able to make a remarkable statement, which happens to be of tremendous importance for your own country. Smallpox has disappeared from assessable areas of the planet, as evidenced from the absence of new, naturally occurring, cases recorded over the last two years. This is a triumph for the World Health Organisation, for all the public health workers concerned, and if he can hear us from heaven, from one of our own Fellows of the Royal Society, Jenner himself, who began it all. It is also a triumph for the modern virologists who have worked on the smallpox virus, its variants, its reservoirs of infection, and the immunizing agents.

In the summer of 1978 however while the World Health Organization was waiting the essential two years with bated breath, a laboratory photographer called Janet Parker developed smallpox in Birmingham, after infection with a strain of virus identified as coming from a nearby laboratory which was working on smallpox for the World Health Organization. Mrs Parkar died, a relative was infected but survived, and the virologist in charge, Professor Bedson committed suicide. Some years before this dreadful tragedy, another series of cases had originated from a virus in a research laboratory in London, and no doubt in the past and in other places there have been similar unfortunate laboratory infections with this dangerous agent.

The Birmingham accident could not be ignored by the Governmment, the Health Authorities, and certainly not the Unions responsible for laboratory staff such as Janet Parker. As a result research on smallpox for World Health Organization has for the time being been terminated in Britain, and in future it will probably be difficult to work without considerable restrictions, even with the disarmed vaccine strains.

Since smallpox has now disappeared, this may not matter unless the virus returns from some unknown reservoir, and smallpox experts in research laboratories are needed again. But supposing there had been the same reaction at the time of the first vaccinations by Jenner, or even in later years as vaccine strains were developed. There must surely have been accidents and unnatural infections, since variolation, which preceded vaccination, was carried out with fully virulent smallpox virus. If public concern about safety was as strong than as now, so that research was effectively stopped, then the elimination of smallpox from the world would never have occurred in 1978.

The same sort of restrictions, which are now operating in the United Kingdom, might also have considerably delayed the research which led to the introduction of poliomyelitis vaccine or before that yellow fever and cholera vaccine. I even doubt if the transmission of malaria would have been demonstrated if Ross had to work under the strict containment facilities required today.

Now, it may be argued that research in these important fields has never been forbidden, only that restrictions have been imposed and essential precautions introduced to protect the staff and the innocent contacts. Surely this is a reasonable requirement, to which it is difficult to object in the face of a potential killer like the smallpox virus. But extreme restrictions do inhibit seriously the free-ranging curiosity in the early stages of an investigation which is the beginning of all successful developments. I simply want to point out that if our predecessors had not taken risks with infectious diseases, from which some of them died, the consequences would have been out of all proportion. For diseases which have been successfully combated in past, more adventurous, times, it is not now too serious a problem. We should be concerned however about those that remain, such as hepatitis, even cholera, and the parasitic diseases. These after all are not a minor problem in India.

Thus far we have been considering the increasingly strict safety regulations which are being introduced to reduce risks to man from detectable and quantifiable hazards, such as microorganisms of known virulence and transmissability. These are cases where dangers are known to exist because accidents have already occurred, and despite my concern about regulations, it would be criminal not to reduce even if we cannot completely eliminate, the risk of further accidents.

I now turn to a much more difficult problem, namely hypothetical risk, where there has been no accident or any other direct evidence of ill effects of a procedure, but where theoretical objections have been raised and the procedure has not been proved to be either safe, or unsafe. It is the type of situation faced by traffic engineers considering whether to place a pedestrians' crossing over a theoretically dangerous highway. Should they go ahead, or should they wait until an accident proves the highway to be hazardous? Curiously I understand that the latter is the normal procedure in our country despite increasing emphasis on safety.

Molecular Genetics

The research field which is now most affected by precautions against hypothetical risks is genetic engineering at the molecular level, using the new recombinant DNA techniques. Since it has introduced a new era of biology of enormous potential and practical significance in relation to some of the threats I mentioned, we should consider it carefully.

Up till several years ago manipulation of genes could only be carried out by allowing natural, usually random, processes, such as damage and reassortment of genes, to take place. In this way genes from one strand of DNA were able to transfer to another strand and perhaps to another host but rarely another species of organism. Success depended on skill in selecting the rare combination desired, whether it be a high yielding wheat, or a good antibiotic-producing strain of a fungus.

This was changed by the discovery of enzymes named restriction endonucleases, which can cut the strands of DNA at identifiable sites, and of other enzymes, ligases, which can stitch free ends of the cut DNA together again. It meant that individual genes could be excised from one host chromosome and inserted into a specific site in the DNA of another host, which could be in a distant unrelated organism.

Apart from increasing the rate of useful rearrangement of genes this procedure had immediately many advantages. First a single particular gene can be isolated and by insertion into the DNA of a fast-growing simple organism such as a bacterium it can be propagated in enormous quantities to produce large number of identical copies which are easy to study. This is the technique of cloning. Not only can the gene itself be propagated and studied, but neighbouring regions of the DNA sequence which exert a regulatory function can be included. Even the working copies, messenger RNA, can be cloned and this has already led to quite unexpected findings about the regulatory processing of these primary copies of the gene, which has upset the old idea that one gene always codes directly for one protein.

Probable Benefits

But not only does this give an opportunity to propagate a particular gene. With new skills which allow the appropriate regulation of expression, the transferred gene can produce its protein product in its new host in large quantities which can be purified easily. Thus insulin and human pituitary growth hormone, which have always been extracted laboriously from animal pancreas and pituitaries respectively, could now be produced by propagating the relevant genes in bacteria, and these bacteria will produce the hormones or their precursors. It is to be expected that hormones can be produced by this method in very large amounts. Other useful products such as a possible antivirus drug, interferon, and purified immunizing vaccines made from virus genes, or antibodies against harmful agents, should be produced in the same way in the coming years.

The ability to move genes around, propagate them, and to produce their products in quantity has untold potentiality. For example, as I have mentioned, one of the major handicaps in food production is the lack of ability of major cereal crops to fix atmospheric nitrogen. The possibility now exists of improving the nitrogen-fixing capacity of the symbiotic soil microorganisms by genetic manipulation, and attempts will be made to introduce known genes, which specify nitrogen-fixing enzyme mechanisms, from bacteria directly and permanently into the genetic apparatus of cereal plants. Perhaps resistance to fungal pests and virus diseases could also be introduced as new hereditary systems in major crops. Finally we may see new food sources developed from lower organisms with rapid growth, efficient conversion of energy, and usable proteins.

It is noteworthy that all these developments have given birth to a new word, biotechnology, to describe the emergence of new fields of industrial development which are already following these, and other advances in biology such as enzyme immobilization. No doubt there will be many obstacles to the full development of useful applications even when the primary laboratory problems are solved, but few doubt the future impact of biotechnology.

Hypothetical Risks and Real Fears

I wish, now, however to consider some obstacles which are before us today and which arise mainly from fear of the unknown. So unprecedented were the developments, and so unknown the consequences, of large scale gene transfer and propagation, that the earliest workers led by Dr. Paul Berg in Stamford, proposed a pause in research for a period, that is a moratorium, to assess the situation. A particular reason for this concern was that the most suitable host organism for isolation and growth of foreign genes happens to be a derivative of the common gut organism *Eschericia coli*. Two types of hypothetical hazard could be imagined.

First it would be theoretically possible to introduce a gene for a poison, such as cholera toxin, into *E. coli*, perhaps along with a series of genes which conferred resistance to several antibiotics. This unpleasant organism might then infect a laboratory worker or even spread to wider population.

Second, the isolation of genes from the original host is not always precise and tidy, and in fact one of the procedures commonly used is to clone the many pieces randomly obtained from fragmentation of DNA from a whole organism, the so called shotgun approach. Unknown and unexpected fragments might contain unpleasant additions such as dormant tumour virus genes which might be propagated and activated in *E. coli* and then transferred by accident to a laboratory worker and perhaps cause cancer.

These and other fears were voiced, and in the ensuing years special safeguards were introduced as a precaution against possible hazards. For example disabled strains of *E. coli* are now used, which cannot survive in the human gut, and it has been shown that even when tumour virus genes are deliberately introduced into bacteria, even though they can be recovered intact, their abnormal situation does not give them any new and special ability to affect an animal. Indeed it may well be claimed that public anxiety has had a real benefit because it has forced scientists to evaluate risks, and take care. Most important it became increasingly clear from general genetic principles, that organisms with abnormal new genes would rarely survive in nature. Actually, the safest way to study a very nasty virus such as smallpox, or a very virulent cancer virus at this time, would probaby be to propagate its isolated genes in *E. coli*.

But though the unprecedented self denial call by Berg and his colleagues in 1974 is now thought, at least by many scientists, to have been unnecessary and the fears unjustified, powerful groups representing various branches of society and public opinion, and even some scientists, have not been so easily persuaded. There is now an entirely new climate of opinion, in which the arguments put forward and supposed to be rational by scientists, no longer carry weight. The very hypothetical nature of the risks, and unpredictability of all the consequences gave rise to uneasy fears, for example of cancer epidemics and other mysterious terrors. Moreover safety is a powerful tool for leaders of organised pressure groups, since it is hard to be against it, even when carried to absurd levels.

Regulations

As a result of the Berg proposals for a moratorium, official government enquiries were instituted. As it happened, I was on the first, chaired by Lord Ashby in the United Kingdom. These enquiries led to other investigations and studies, and finally to classifications and codes of practice for experiments involving recombinant DNA. They have been introduced by now into most countries of Europe and North America with variable control by non-scientific authorities and the law itself. Most of these countries now follow the guidelines introduced in the United States, while Britain has recently introduced a new type of assessment, based on attempted quantitation of risks. Almost alone, the United Kingdom regulations are enforceable by law. All experiments involving the transfer of foreign DNA from one organism to another have to be notified (even in some instances if a gene is taken out and put back into the same organism, so-called self-cloning). Special permission and protective procedures are needed for categories of supposedly higher risk. The trouble is that there has never been an accident or ill effect so there are no risks to quantify as higher or lower, and the scale is therefore arbitrary.

After early very restrictive regulations and codes of practice, more realistic appraisal has during the last year or so led to some relaxation of the requirements, particularly in the USA and countries which follow their procedures. Britain has also seen some sensible changes though it remains still relatively more difficult to do potentially useful work leading for example to the production of a protein product, especially in large quantities.

Further relaxation may occur but it only requires an accident, or a statistically insignificant but newsworthy appearance of an unusual illness, and the pressures for increased restraints and the halting of particular research programmes will mount again. Fortunately the apparatus for control which now exists may in these circumstances held to ward off unsupportable criticisms and by preventing panic be an advantage.

Other Fears and Benefits from Current Biology

I wish to return finally to the consequences of these and other controls in research, but let me first point out briefly that there are other fields, where public opinion has been aroused against the consequences of research by biologists.

There are for example the other sorts of genetic engineering, concerning reproduction, especially where applicable to humans. They include *in vitro* fertilization of ova, implantation of fertilized ova, and foetal sexing (all of which have already been accomplished), and perhaps, for the future, genetic manipulation of ova and sperm. Despite possible medical benefits, none of these potentials for research in reproductive physiology make the scientists concerned very popular. There are also the sociobiologists whose studies on breeding and so-called Darwinist behaviour are opposed as encouraging racism.

In Britain there are well-organised groups of animal lovers who are deeply opposed to the use of any animal in scientific research. In fact legislation is now before our parliament which may put severe additional restrictions on work involving animals of any sort.

There are the worries which have been expressed about the collection and storage of data about individuals, in large scale epidemiological and statistical research, because there could be a threat to the privacy of the individual.

All these add to the other forms of disaffection for science which is apparent in many advanced countries just at a time when the demands on science to meet the threats of the coming decades are mounting.

Conclusion

To conclude, let me return to the general problem of risks and benefits of research.

There is no doubt that a Government has a duty to protect its citizens against dangerous practices by any group of inhabitants, however well meaning the latter may be. In the case of research with a highly dangerous organism such as smallpox, or some of the rare exotic virus, no one would forgive a scientist or an employer who did not take every precaution, particularly to prevent harming the innocent, and perhaps unknowing, bystanders, including the technical assistants. But should the experimenting scientist himself, if he instigated the research, be forbidden to take risks even in these circumstances? Presumably yes, if his own risk increases that of others, but not necessarily if the scientist concerned could alone be affected, and he was fully aware of the hazard.

Smallpox and similar conditions are extreme cases. What about cholera or typhoid? In our country these rightly require protection systems. Some cancer research, and particularly work on leukaemia, may be subjected to restriction, because blood and other tissue from patients under treatment must be in containment systems in case of risk of hepatitis. These are all sensible precautions but we should remember that they are obstructive to research.

The problem becomes more difficult as the risks become more indeterminate and unquantifiable, such as those we have discussed as arising from recombinant DNA techniques. But for even the remotest danger the common response is naturally to play safe, and to demand safety procedures, which would be needed for work with better known hazards. "What is there to loose?" It may be said, "Your research is not forbidden; you must just do it in certain way". But there could indeed be something to loose from excessive and only questionably necessary safety precautions.

First take the direct costs. The type of safety facility now required in Europe and North America is becoming increasingly expensive as rules become more and more stringent. For example approved safety cabinets, which are not cheap, have to be replaced frequently as approved specifications are changed, and large scale isolation facilities are very expensive. There is also the large indirect cost in staff time, especially that of highly trained personnel, since each operation takes longer to do in the special containment facilities. (One might also add the time spent in meetings of safety committees). Money spent on safety seems to go into a bottomless pit, while of course it could be used on other things, including research itself. And what are research workers in less wealthy countries supposed to do? Eschew work on pressing local problems because of distant safety rules?

Second there is the effect on free enquiry and on the choice of research programme. Other things being equal, when faced with a choice of problems, most scientists will choose one which can be solved quickly, and without restriction. There is likely to be a selection against problems, however important, which could lead to interference with freedom of enquiry, and where regulation can be forseen. It might, on a different scale, even affect a choice of careers in science.

Thus there is another side to the coin, a drawback to safety precautions which has to be set against the gains. Unfortunately we cannot set the gains against the losses in the form of a cost-benefit analysis, particularly in topics like genetic engineering, since social fears and anxieties and even real risks, however low, are unquantifiable. But if we scientists are forbidden to take any step in the dark, into the unknown, until such a move is proved to be free of hazard, then it is not only scientists, it is the whole human race which will suffer.

Mr. President, I have been discussing prevailing attitudes and trends, and possible obstacles to research in Britain and other western countries. What has this to do with science in India?

The problems which face you, your expanding population, your agriculture and disease problems, are gigantic, but you already have a strong and developing tradition in many fields of research. I hope, during my present visit, to learn not only about some of this research but also about social and political attitudes, particularly towards the biological sciences, and in passing your views on possible hazards from research.

There is perhaps some loss of nerve and spirit of adventure in the west, not amongst the scientists themselves, but in our society's attitude to exploration of the unknown. This may adversly affect the quest for new knowledge, which will be vital for your own future well-being as much as ours. In the end the responsibility for exploring new horizons will pass increasingly to you, and I conclude with the hope that research in India will be as free as possible from the constraints I have been discussing.