WHO Forum June 1976 12-17

risks and rewards

Dr Martin Kaplan, who heads WHO's Office of Research Promotion and Development, was the moderator at a special round table discussion on biomedical research arranged by World Health. With him were Professor B. O. Osuntokun, Dean of the Medical School of Ibadan, Nigeria; Professor Joshua Lederberg, Professor of Genetics at Stanford University, Palo Alto, California, USA, a Nobel laureate; and Professor Jacques Monod, Director of the Institut Pasteur in Paris and also a Nobel laureate.

KAPLAN: Professor Osuntokun, in which fields of public health do you feel that research is most important for the diseases that you encounter in West Africa?

OSUNTOKUN: In the developing countries, particularly in the tropics, we face severe problems from communicable diseases aggravated by malnutrition. These are the areas in which research into public health can contribute tremendously towards ameliorating morbidity and mortality in these countries. It has been calculated that if we can eradicate or limit the morbidity and mortality imposed by 12 named diseases, we can reduce the mortality and morbidity in these developing countries by 95 per cent.

KAPLAN: Here is a group of diseases in which research has been going on for many years, and yet it is apparent that we are far behind in having the available tools to combat them effectively. We have been attacking malaria, for example, for the last 10 or 15 years with insect control and have made great inroads, but we have come up against a very difficult problem in Africa where social and economic conditions preclude using such means. If we had a vaccine against malaria, it would be a very marked improvement. How can we go about developing such a vaccine?

LEDERBERG: I would not want it taken for granted that vector control is not part of our strategy. The situation requires much more careful examination to determine just what measures might be used. However, it is true we have tended to place almost excessive reliance on one simple technological solution. DDT was going to be the miracle that would solve this problem once and for all, and while it did for a time have nearly miraculous results in some parts of the world, it is now apparent that a much more complex approach is necessary. I would agree that until we can be sure that we have alternative approaches by vector control, a direct attack on a malarial parasite and an understanding of its biologies is an extremely important step to take. One reason for the relative neglect of the biology of parasites during the past 20 years has been the temporary success of methods based on vector control. Only now when we see these have not worked out effectively do we realize that we must go back to much more fundamental approaches.

KAPLAN: Professor Monod, your work in the field of molecular biology won you the Nobel Prize, yet it is difficult for many people to see how this can be directly related, or what promise it might hold for solving such fundamental biological problems as parasitic diseases.

MONOD: Let me begin with a field that is not mine, namely parasitic diseases again. I think all approaches must be used at the same time and I agree with Dr Lederberg that, for instance, vector control might be sought for or achieved by means other than chemicals. There is much more work to be done in developing preventive means, such as vaccines, but recent work in our Institute suggests

Round Table discussion on biomedical research at WHO headquarters in Geneva. From left to right: Professor Jacques Monod, Dr Martin Kaplan, Professor B.O. Osuntokun, Professor Joshua Lederberg. (*Photo WHO*)

that parasites have very special ways of defending themselves against the immunological defences or organisms which are successful for, say, viral diseases or microbial diseases. Some very important advances may be made in this field in the next five years.

KAPLAN: Suppose we did have effective vaccines: the problem is how to apply our knowledge under difficult local conditions such as one finds, for example, on the African continent.

OSUNTOKUN: The greatest constraints in applying knowledge and improving the delivery of health care, as far as the African continent is concerned, are constraints dealing with the availability of manpower, and of course, ignorance which can be corrected by health education. In most of the developing countries, you just don't have the manpower to go around and apply things like immunization. This is an area in which we have to do something fairly quickly if we are going to benefit from the rapid advances in medical knowledge.

KAPLAN: Lack of manpower is certainly one of the most severe constraints, and particularly the lack of research manpower. That is one of the reasons why we in the World Health Organization have launched a special programme of research in tropical diseases (see article by Dr D.S. Rowe in this issue) to try to build up a research manpower base in the developing countries.

LEDERBERG: Very much depends on the time scale that you feel is important to achieve significant progress, and all these problems are interconnected. The health status of the country influences its economic productivity which in turn influences the availability of capital for investment, in human resources as well as other industrial resources. These matters are all completely interlinked. Now you can view parasitism with malaria as a well-established ecological equilibrium. It is not a very satisfactory equilibrium from the human standpoint, but we have the mosquito, we have the parasite, we have people; they have found themselves in a particular circumstance which will be stable (to the human detriment) over a considerable period of time, unless we do something about it. Any large-scale disturbance that we make of that equilibrium involves some risk. It is hard to think of any method of altering the situation which might not have some side-effects. Certain side-effects followed the introduction of DDT, for example, but I am sure the hazards to human health of DDT are much less than the benefits in those zones where it has been effective as a public health programme.

KAPLAN: Your point about possible risks recalls one of the most heated controversies of recent years, concerning the so-called genetic manipulation of micro-organisms; there have been some

◁*Student nurses at a training school in Gabon, West Africa. Unfortunately, in most of the developing countries of Africa, there is simply not enough manpower to meet the health needs of the people.* *(Photo WHO)*

A patient being treated in a Sudanese hospital ▷ *for sleeping sickness. The disease is caused by one of the parasites whose life-cycles we need to understand better if we are to control them.*

(Photo WHO/D. Henrioud)

horror stories thrown around that this has untold dangers for mankind. We would like to know more about this procedure and how you view its future possibilities.

MONOD: These hazards exist. Whenever a new powerful tool is developed in fundamental science, new knowledge is new power, and new power can be put to good use or to ill use. But there is nothing specific about this particular development, in fact I think that it is far less hazardous than many that we have seen or will be seeing in the next few years. Microbiologists around the world have learned over the past 100 years or so since Pasteur's work to handle extremely dangerous pathogenes in complete safety. The kind of hysteria that has developed recently – simply because the public has been poorly informed – reminds me of what happened when the Pasteur Institute was first built in Paris. A number of articles appeared at that time treating Pasteur as a sort of Frankenstein monster who was going to spread horrible foreign diseases around the city. It's the same story today. Frankly, there is much less danger in most of the research programmes now under way in this field than there was at the time microbiology began, and we have only to look at the benefits of microbiology. These new techniques of genetic engineering have a wide variety of application, not only in medical therapy, or prevention, but also in zoological technology and agronomy; they may contribute considerably to solving some of our nutritional problems.

KAPLAN: Professor Lederberg, you are a geneticist. Can you give as simple an explanation as possible of what *is* genetic manipulation?

LEDERBERG: All the findings of molecular biologists for at least the past 25 years focus on the way in which genetic information is represented in a chemical substance at the centre of a cell. This chemical substance is DNA. And while we have had a revolution in our biological understanding of the nature of life, the cell, reproduction and the mechanism of evolution, up to now this has had very little actual medical application. DNA, deoxyribonucleic acid, is the substance in which the genetic information is represented and forms the material basis of the gene. It is a chemically defined structure of considerable complexity, the blue-print of the cell. If you put DNA into an animal, or inject it into a man's veins, unless there were some very special circumstances where the DNA was taken directly from an infectious virus, it would have no biological activity whatsoever. Only in experiments with micro-organisms, with bacteria and with certain curious particles found in bacteria called plasmids, have we found operationally effective ways of demonstrating that DNA does have biological specificity in revealing the information which is present in that DNA. This means that the focus of technical application of our basic scientific knowledge about the structure of DNA is still limited to those cases where DNA can be used as a reagent, having some effect on the biological outcome of the system into which it is introduced.

KAPLAN: What benefit has medicine had

so far from this molecular engineering in terms of prevention of disease?

LEDERBERG: So far, very little.

MONOD: As Professor Lederberg says, there are still few ways of applying the basic knowledge and concepts of molecular genetics, of molecular biology. On the other hand, great benefits have been derived from technical advances stemming from this work, for instance, most of what we know and understand about virus replication structure and so forth comes from this work and it has been very important in the development of modern viral vaccines.

LEDERBERG: What are being developed—which in the long run will totally transform the picture—are methods whereby DNA from one cell, from one source, can be implanted into the genetic structure of a totally different kind of cell. Thus it has been possible to move DNA not only from one strain of a common bacterium *escherichia coli*, into another of the same species, but even very different strains of bacteria, and even totally unrelated organisms. For example, one can take DNA from the cells of a toad, and certain special kinds of DNA in such cells can be implanted into a bacterium and used there in order to manufacture large quantities of products that originally came from the toad. This opens possibilities for very important applications in just the sphere that we are talking about. Many of the parasites against which we are trying to produce vaccines, whose life-cycle we need to understand in order to control them, are very difficult to deal with in the laboratory, precisely because they are hard to cultivate. It has been a major obstacle in the study of malaria that we do not have a pure chemically defined system in which the malaria parasite can be grown in the way that we can grow bacteria. We have to grow it inside the living red cells of certain hosts, and even then, there are severe problems. One possible method of producing purified vaccines, which I am sure will be attempted in the very near future, would be to isolate fragments of DNA from the malaria parasite and implant portions of that DNA into bacterial clones. Those clones (identical progeny of a single cell) would then be examined to see whether any of them produce products that can be used as vaccines against malaria. This would be a prototype of a wide variety of experiments that are available to us now and simply could not have been done two years ago.

KAPLAN: One of the hazards that has frequently been mentioned is that, for example, by taking a cancer virus that is known to produce a cancer in animals and then isolating the component of the DNA responsible for producing the tumor and putting it into a cell, we could reproduce large amounts of the virus. If it escaped from a laboratory, it could be spread widely among the public. Is this a matter for concern?

MONOD: This is just the kind of speculation that has tended to frighten people. In fact, while the remote possibility of something of that kind happening has to be borne in mind, the techniques and security measures to prevent such an event or to contain any dangerous organism that might turn up are well

known and can easily be built in at relatively little cost. The risks involved in the use of these techniques have been greatly exaggerated.

LEDERBERG: I agree with Professor Monod and would like to add that the very term cancer virus scare is a misnomer. The public would be misled if they thought a wide variety of infectious agents existed which were known to produce cancer in man, in the sense that there is a virus for influenza, and a virus for measles, and so on. That kind of a virus for cancer in man does not exist. We have evidence that certain viruses, when inoculated under very restricted experimental conditions into newborn mice or newborn hamsters at a time when they have no immunological protection whatsoever, can induce widespread tumours. This is a very interesting biological phenomenon and is expected to shed light on the problem of cancer formation. But the viruses capable of having this effect are already very common in nature—one or two per cent of all wild rodents already carry the polioma viruses, a large fraction of wild monkeys carry the S.V. 40, and some very common viruses of the adenal virus group, which cause respiratory and intestinal infection in man, have been shown to have cancer virus-like properties and are present in perfectly healthy people.

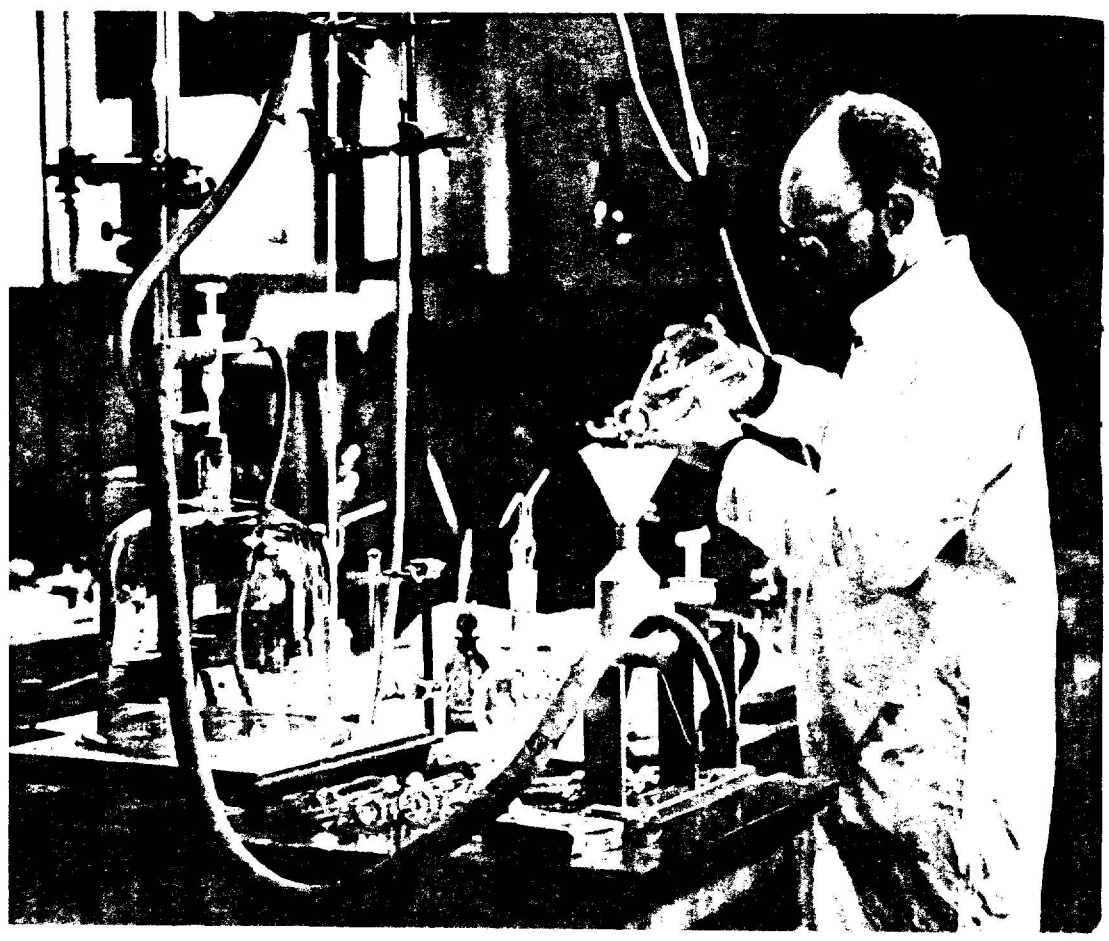
KAPLAN: And there has been no evidence as yet for the transfer of tumour viruses from animals to man: they seem to be quite species specific?

LEDERBERG: They do, and we may indeed be thankful that this is the case, because of our daily exposure to agents of that kind. Many viruses may contribute to the possibility of cancer developing in the individual, which makes it all the more important that we understand their mechanism. The risks are there. For example, as an approach to dealing with the problem of cholera, one might wish to undertake new combinations of genes, including those for the toxin of cholera, and to put it in a different biological framework, like that of an otherwise harmless *escherichia coli*. It is quite possible that such things could be produced and that, if they were, they would multiply the cholera problem because there would be a variety of kinds of organisms capable of giving the symptomology of this disease. But as Monod said, such a level of hazard is already an important part of medical microbiological research, and it would be madness to

Above: *Louis Pasteur (1822-1895) was widely considered as some kind of Frankenstein monster who was going to spread horrible foreign diseases when he opened a research institute in the centre of Paris.*

Below: *Today, the Pasteur Institute in Paris is one of the most respected research centres in the world.* *(Photos Institut Pasteur and P. Almasy)*

Right: *Rehydration fluids being administered to a baby with marasmus, whose mother has another deficiency disease, goitre. New techniques of genetic engineering may contribute to solving some of the world's nutritional problems.* *(Photo WHO/E. Mandelmann)*



put a stop to such research. It would be folly to allow it to continue if there were not reasonable precautions connected with the circumstances in which it was done. A large part of the public outcry about research which is labelled *DNA recombinant research* arises because a new community of investigators are now working in this area. These are people whose prior training has been in fields other than medical microbiology and, in a certain sense, they have now discovered it for the first time. This is a very fortunate circumstance. It brings in enormous additional intellectual resources, but there is also a certain element of enthusiasm when they first encounter the kind of risks we are discussing.

OSUNTOKUN: Could there be some religious tone to the fears that maybe scientists these days are now creating life out of nothing?

MONOD: I am sure that is so. In the years since the great discoveries in molecular biology, there have been discussions in the press about the possibility of manipulating the genetic structure of man, and creating a monster, or what not. Of course, what we are talking about now has absolutely nothing to do with that, and I think it is important to point it out. Even the word genetic manipulation is unfortunate. There is something ominous about it. The expression genetic engineering is preferable.

LEDERBERG: This is not to say that there are no risks to the microbiologists themselves. There are heroes in the field. And again, there have been unfortunate incidents which we can trace to sloppy techniques. We have to be careful that microbiological research is done to a high standard of care and concern, so that we don't have a repetition of such incidents. The risk is if we neglect elementary precautions. If we stop research in this direction, we shall pay a heavy cost. The enormous benefits from microbiological research are already very well established. Hundreds of millions of deaths have been prevented by the knowledge that has accumulated during the past century, and there are prospects of being able to do the same by continuing this research. And those are benefits of such magnitude that I think no-one who examines the situation will want to forgo them in the face of the very speculative and hypothetical risks that have been suggested about research in this area. ■