ECONOMIC AND SOCIAL COMMITTEE
OF THE EUROPEAN COMMUNITIES

GENETIC ENGINEERING

COLLOQUY

Brussels 1981

On 14 and 15 May 1981, the Economic and Social Committee of the European Communities, under the chairmanship of Mr Tomás Roseingrave, held a colloquy on "The Safety Aspects of Recombinant DNA Work". The colloquy was chaired by Mrs Hedda Heuser, Rapporteur for the Economic and Social Committee's recent work on the subject.

The idea of the colloquy originated within the Economic and Social Committee in an Opinion and Study drawn up in 1980.

ECONOMIC AND SOCIAL COMMITTEE
OF THE EUROPEAN COMMUNITIES

GENETIC ENGINEERING:

SAFETY ASPECTS OF RECOMBINANT DNA WORK

Colloquy organized by the
Economic and Social Committee
on 14 and 15 May 1981
in Brussels

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PREFACE

Genetic engineering is a rapidly developing field. It touches many facets of our economic and social future. There is thus a need to stay abreast of developments. This applies equally to the public authorities, the different economic and social interest groups and, indeed, to society as a whole.

Accordingly, the Economic and Social Committee of the European Communities organized a Colloquy on "The Safety Aspects of Recombinant DNA Work" in Brussels on 14 and 15 May 1981. The participants included representatives from the fields of government, science, industry, trade unions, consumers, environmentalists, religious, youth and women's groups. The discussions took place within an "information-exchange" framework. No policy conclusions were drawn. It is hoped that the information provided in this way, and which is contained in this publication, will be of assistance to the different European Institutions and interest groups in their future work.

The idea of the Colloquy originated within the Economic and Social Committee in an Opinion and Study drawn up at the end of 1980. The Study, which describes the general background to the subject and sets out the Committee's initial views, is provided in the Appendix.


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OPENING SPEECHES

Mr Roseingrave,
Chairman of the
Economic and Social Committee:

Representing the cross-section of the socio-economic interests in Europe, we, in the Economic and Social Committee, have always found dialogue and debate to be a valuable and constructive experience. It is our central role to act as a meeting point for the social partners at European level. We are therefore glad to be able to extend this approach to the biological sciences and to learn something of the influence they will have in economic and social activity in the future.

If biotechnology emerged at a time in the 1970's when society's attitudes to scientific and technological development were already undergoing a fundamental change, with a questioning of development for its own sake and the preoccupation with possible negative effects, it was also a time when growing demands were being made for immediate practical, social benefits, for new industry, new sources of energy, solutions to environmental problems, raw materials, improvements in health, and the whole concept of "*the quality of life*".

In the work of the Economic and Social Committee these concerns and questionings come through very clearly and consistently in recent years. They are still to the forefront of our minds. Our hopes and fears, perhaps understandably, led us at times to expect too much, to look for panaceas for our pressing problems from the new biology, or on the other hand to see only in it a detrimental development of scientific knowledge. But a realistic assessment is now needed so as to avoid these extreme viewpoints. Because of the future importance of biology, we now need a deeper understanding of the main issues involved and their consequences for human society.

We need to know realistically, or at least with some acceptable definition, what benefits to expect and within what timescales they will be available. We need a sound assessment of the risks involved. We need to know how these advances in science and technology can be handled to protect society's best

interest, and the rights and dignity of man. That is the first purpose of this meeting.

At the same time, to create a climate in which the research and innovation processes can respond with maximum effectiveness to society's needs, a broad social consensus is required. We need first of all to have a clear idea of our economic and social goals. We need a commitment to the research effort needed to achieve these goals. We need an agreed view on ethical questions. And we need appropriate guarantees against technical risks. It is our belief in the Economic and Social Committee that this meeting can contribute to this process. We hope in this way that it will be a particular help to public policy makers and administrators, to science and to industry. That is our second aim.

In promoting a dialogue on these issues at European level, we do not wish to take away from the work of the different Community and national bodies which are active in this field. Rather it is our hope that all institutions and interests will be able to benefit from this two-way flow of information which they can then use in their respective future activities.

At a more general level, you are helping, through your work, in the construction of Europe. To achieve it, it will demand courage and dedication to scientific investigation. We all hope that it will be a better Europe, a Europe to which this colloquy will have made its own significant contribution. I wish you every success.

I have much pleasure in declaring this colloquy now open.

Mrs Heuser, Chairman of the Colloquy:

The work of the Economic and Social Committee mostly consists of pooling its members' knowledge, experience and interests in order to reach a consensus on certain key policy issues submitted to it and finding politically feasible ways of getting Europe to work. We are not always totally successful in this aim, either because the obstacles are too great or because special knowledge is required before any decisions can be taken.

Experts are a help. But they can only partially remove this feeling of uncertainty. The more one gets into a contentious issue, the more one becomes sensitive about taking responsibility for something about which one has insufficient knowledge.

The Economic and Social Committee became aware of this when it first tackled the question of genetic engineering. When it finished its work it thought that it was not proper for a body of its kind to keep knowledge about such an important topic for the future restricted to a small handful of people.

The decision to draw up a Study was unanimous, and there was also strong support for organising a hearing like the one we are holding today to gather further knowledge and debate questions which were still open. Our Study showed us that we should start with the premise that genetic engineering today can no longer be considered merely as a method of biological research. It has been estimated that in my own country alone there are some one thousand research projects going on at present. As the European Community sees itself as being forced to run in a world-wide race as regards research and its industrial application and has set aside great chunks of its budget for a research programme, we should ask ourselves whether the present optimism about genetic engineering is justified, whether the cost/benefit ratio is reasonable and whether all possible risks have been considered.

The question of the possibilities and risks of genetic engineering has, of course, been taken up and discussed many times by researchers themselves. But this has still not prevented sensational publicity from having lasting consequences. Even if, after ten years experience of genetic engineering, we can believe that these fearsome scenarios will not come about, we must still ask ourselves whether we can really always assume in the future that genetic

engineering work is harmless, that safety measures really are safe and that the human quest for knowledge will stop at ethical barriers.

Mr Roseingrave has already said what the aim of this colloquy is. For me it is particularly important that we air all our differences here, however diverse they may be. Our aim cannot be to "*achieve*" a common viewpoint. I should also like to note that this is the first international forum where scientists and socio-economic groups have been able to exchange ideas on genetic engineering.

TOPIC A: DEVELOPMENT POTENTIAL

Mr Richards, Rapporteur:

It has been suggested that great new benefits will flow from the application of recombinant DNA technology. It is argued that these benefits will not just be new things but also newer ways of doing old things. To make an accurate assessment, the questions must be asked: what has already been achieved at scientific level, and when will these benefits become generally available to the public.

The first area of scientific advance is in the general field of health care, improving our ability to deal with disease. There are several categories of activity. Among the first of the new potential drug therapies to be the subject of cloning and expression in bacteria, is human recombinant insulin. Work is well advanced. At least one company is developing a manufacturing process for human insulin in both the United States and in Europe. Most people suffering from diabetes are dependent on daily supplies of animal insulin. But sources of animal insulin are becoming more difficult to obtain. At the same time, it is needed on a greater scale, particularly in developing countries. An alternative source is therefore needed. It is also hoped that human insulin, being the actual human hormone and not an animal hormone, which is slightly different, would have fewer longer-term side effects. But this has yet to be proven.

Human growth hormone, which is also very important, has also been successfully made in bacteria. At present it can only be obtained with difficulty from human pituitary glands and is therefore in extremely short supply. Manufacturing processes are being set up in both the United States and in Europe. Chemical testing is just beginning. Several other hormones are also being developed which will help to tackle diseases which could not otherwise be handled, particularly in the immunological area.

Another important category is the combatting of virus disease. Some virus diseases are just inconveniences. Others are of serious economic consequences. One example is that of serum hepatitis, caused by the virus of

hepatitis B. It is serious in that it exists worldwide. It has the peculiar property that it is present in a large number of people who carry the disease in their blood, but do not themselves show symptoms. If their blood is used for transfusion, or if they are in contact with other human beings who are not so infected, these people may get a serious disease which can result in death. There is some scientific evidence which also suggests that people who are chronically infected with this virus may progress towards liver cancer. Conventional approaches to produce a vaccine for hepatitis B have failed. One of the reasons is that it has not proved possible to grow the virus in tissue culture outside the body. Without the new technologies, there would be little possibility of producing an effective vaccine. Two of the important viral antigens, which might form the basis of an effective vaccine, have already been cloned and expressed in bacteria.

Influenza is another virus disease which everyone has contracted at some time or another. It is not serious for the individual. But its economic impact worldwide is enormous. It can also be lethal for the elderly. One of the major scientific problems which has to be overcome is that the disease can vary from year to year, the so-called serological variation. In the case of at least one animal influenza, one of the components of a vaccine, animal influenza surface antigen, has been made and expressed in bacteria. It is also hoped to recombine the genetic material from different serological variants so as to produce an antigen which would form the basis for a more universal kind of vaccine. It is not yet a scientific reality.

Recombinant DNA processes are also being used to develop vaccines against rabies and foot-and-mouth disease in cattle. The first is lethal to those unfortunate enough to get it. Foot-and-mouth disease is economically very important to the food industry.

At a time of growing pressure on the world's capacity to produce high-quality foodstuffs, the new technologies will undoubtedly be of great value. Recombinant DNA technology has already been used to significantly improve one of the processes for making animal feeds based on methane-consuming bacteria. The technology has also been used to produce a sweetening agent which will be better and safer than saccharin. There will be other new therapies based on the natural human materials which will help to counteract stomach ulcers and various types of auto-immune disease.

The Chairman of the Economic and Social Committee referred to several other important areas including the development of new energy sources. Here, it is hoped to develop techniques which will have two important characteristics. Firstly, they will produce fewer waste products and therefore will not pollute the environment. Secondly, they could also be specifically developed to utilize waste materials from other sources, or other plentiful material for which there is no alternative use. On the environmental side, it is

hoped to develop new means of fighting pollution from existing industrial processes and also to develop industrial processes which will produce less waste.

The production of new varieties of plants and animals is another new area which is now beginning to attract serious attention. New plant varieties will be developed to produce higher yields and to grow in a wider range of climates. This may well be very important in areas of the world where, at present, crops can only be grown with great difficulty and with poor yields.

Finally, there is the prospect, although it is only a prospect, of being able to correct genetic abnormalities in people, animals and plants. The first kind of inherited diseases which are likely to be tackled using this technology are those such as sickle-cell anaemia and thalassemia. Advances are more likely in these areas because the technique can only be applied to problems where the scientific basis has already been analysed and understood.

Having looked at the possible benefits, we must also ask ourselves: are there really harmful possibilities. I can only give you my view as a scientist. Following the early concerns expressed by the public and scientists about the possible dangers of these technologies, a number of well-designed experiments were undertaken. They were carried out under highly-contained conditions in case there was some harmful aspect. They tested the possibility of making dangerous pathogens. Essentially the attempts failed. One of the reasons is that too little is known about the scientific basis of pathogenicity.

While I hope the discussion will focus on the potential future benefits, we must not forget that the absence of possible hazards has not been proven. Most scientists now consider that accidental harm is a very remote possibility. We do not know at the moment whether it may be possible to do harm by intention. But at the present stage of knowledge, it is much more difficult to use recombinant DNA techniques to do harm than to do good.

DISCUSSION

Mr Herbig:

Dr Richards has given us a very comprehensive introduction. Undoubtedly there are positive applications. Yet this very significant potential for introducing new products and processes is presented as a simple aggregation of technical possibilities. For example, it includes the production of new and better medicines to combat disease.

Yet, it is not sufficient simply to use the new technology to combat existing ills. The sociological and environmental causes have also to be tackled. Similarly, the possibility of new plant strains reducing the problem of world hunger has been mentioned. Hunger is also due to sociological factors. The technologies currently being developed by large undertakings in the industrialized countries are not suited to the type of agricultural improvement and social change that the developing countries most urgently require. Technical

progress should be looked at, not in isolation, but in the light of social requirements.

Mr Stewart:

It seems to me misleading to state that the majority of diabetics need insulin. In many cases, it is contra-indicated because they produce their own insulin. Injecting external insulin only blocks their own production and makes it a hard drug. The suggestion that animal insulin might be in short supply is somewhat surprising if we look at the number of pigs slaughtered annually.

Mr Bonety:

In his written paper, Dr Richards stressed the importance of a debate between industry and the public authorities. There is however one major omission, the ultimate users of the new technology. We live in a society where new techniques are transformed into industrial applications and then commercialized for financial profit, which does not always represent a gain for society. Since there is still a question mark on risk, it is essential to involve consumer organisations, local authorities, etc. in all discussions between science and industry. This is the only way to ensure that the public is properly informed and that adequate safety precautions are taken.

Mr von der Decken:

Is it enough that it should be more difficult to use genetic engineering for evil purposes than for good? History has shown that this is not sufficient to prevent the harmful application of technology. We must therefore face the question of possible misuse and be prepared to take any measures necessary to prevent it.

Mr Richards, Rapporteur:

Most of my time is devoted to doing things which will hopefully be useful to mankind. I spend little time worrying about possible harmful applications. However, I did mention at least one such possibility. Some kind of pathogenic virus or bacterium might be created which we do not have the means to control. We know that certain characteristics need to be present in order that bacterium might have some pathogenicity. But because the scientific basis of pathogenicity is poorly understood, we do not at present have the means to attempt to create such organisms.

Another case would be interference with organisms whose genetic characteristics we did not understand. But there too, we have no means at present of attempting to intervene.

I agree with Mr Herbig that we should come to grips with the general economic, social and environmental factors which are the source of much human discomfort. If he could identify ways in which RDNA technology could be used to alleviate broader societal problems, I am sure that scientists would be only to happy to apply them. However, a realistic assessment of potential future applications can only be based on scientific achievements to date.

The question raised by Mr Stewart completely confounds me. When Banting and Best discovered the therapeutic value of insulin, I was not aware that they were in fact prescribing a therapy for diabetics which does them no good. My understanding of medical opinion is that insulin therapy can be very beneficial to people who would not otherwise be able to lead any kind of normal life. The future supply of animal insulin and the relative cost of human insulin will ultimately be determined by the economic process. Mr Stewart also questioned the relative therapeutic value of human as opposed to animal insulin, as it differs only in one amino-acid. This is a scientific question which will be answered in time.

Mr Nau:

I have three questions to put to Dr Richards. What leads him to believe that existing vaccines against hepatitis B are not effective? Why did he not mention interferon? Could he specify the *"other"* hormones which have been cloned and expressed?

Mr Richards, Rapporteur:

It is very remiss of me not to have mentioned interferon, but it has had so much publicity that I thought that everyone here would have already formed their own views. Interferon has been cloned and expressed by at least six different groups both in industry and in academic laboratories. There have been some interesting surprises. We now have a range of interferons each of which may have some specific therapeutic value. We also have the means to make these interferons in significant amounts. Clinical studies are beginning, using recombinant interferon from different tissue sources. There have been many claims for its enormous therapeutic value. I am not aware of any demonstration to date that interferon will be an effective anti-cancer agent. There is no doubt, however, that it is an effective anti-viral agent.

To reply to your second point. I do not think I said that the hepatitis B vaccine was not effective. What I did say was I do not think it has been of demonstrated effectiveness. Briefly, it is a vaccine which has been produced by purifying the surface antigen of the hepatitis virus which exists in the blood of carriers. It has been available for some time, but I am not aware of any scientific results. Maybe Dr Gartland can tell us more of that.

With regard to the other hormones which have been cloned and expressed, I can only mention those which are publicly known, since I am not involved in areas which may still be confidential. These are somatostatin and alpha-thymosin-I. There may be others. Perhaps Dr Gartland can bring us up to date on things in the United States.

Mr Gartland:

In relation to the hepatitis B vaccine I am not aware of the current situation or that any tests have been completed.

On the question of other hormones, there is also bovine growth hormone. I think that is about the current list.

Mr Stewart:

I apologize for coming back, but I think that the disagreement with Dr Richards is significant. He assured us that the normal economic process will determine whether human insulin is manufactured in large quantities. That is exactly what I am worried about. Pharmaceutical companies possess highly sophisticated and effective marketing techniques. If a firm has a monopoly, this can lead to the sale of products at substantial profits, without necessarily being of genuine social benefit. Take, for example, the dangerous overuse of antibiotics in many countries where they are not properly controlled.

Mr Coutinho:

The hepatitis B vaccine which is now being tested is made from blood from human carriers. There have been several results which show that it is effective. The important issue is that, at the moment, the vaccine is in very limited supply. This means it will be expensive. As things stand at present, it is beyond the reach of the Third World countries, the ones who need it most. If recombinant DNA offers another way of producing the vaccine, that would be an important step forward.

Mr Fiers:

There are clearly two types of diabetes: juvenile diabetes and that affecting older age groups. It is indisputable that those affected by the juvenile type have, perhaps as a result of a viral infection, a deficiency in the beta-Langerhans cells which are responsible for insulin synthesis. It is equally undeniable that countless lives have been saved by the development of animal insulin therapy. The future availability of animal insulin is indeed an economic question to which I do not know the answer. Nevertheless, it is known that 5 to 10% of these diabetes patients have an immunological reaction to animal insulin whether derived from pigs or cattle. The development of human insulin is extremely important in these cases. Here, recombinant DNA offers the only means of producing sufficient quantities.

To claim that overdoses of insulin will ultimately lead to addiction is stretching the facts too far. Research is currently being carried out in many laboratories into the interactions of insulin and the receptors on the cells. At high concentrations, there is a reduction in insulin response. It is still an open question in scientific circles whether this is in fact a form of negative cooperation or whether it is simply due to an artefact. Needless to say, that it is of little help to patients who are suffering from a serious form of diabetes.

Hepatitis B is a significant problem for us, even more so for the Third World. Patients' blood is clearly a limited source for vaccine preparation. Furthermore, the vaccine produced from it is very expensive. The vaccine

must be inactivated. The tests to prove it so are extremely expensive. They must be carried out on animals like chimpanzees, a practice which might be ethically questionable in large-scale production. Recombinant DNA on the other hand offers a much cheaper way of obtaining adequate quantities of hepatitis B vaccine. However, the last word has not yet been spoken. Much of the present discussion could be superseded by an alternative approach, making vaccines through the synthesis of small peptides.

Mr Thorley:

Current supplies of animal insulin are obtained from the glands of both pigs and cattle. There is no doubt that over the next 15 to 20 years, the supply of these glands will be outstripped by the number of people requiring insulin therapy throughout the world. Many diabetics in the Third World are not able to receive any kind of therapy at the moment. As these countries develop, the demand for insulin will increase and the supply will become inadequate. An alternative source is needed. Recombinant DNA appears to offer the best possibility.

There are undoubtedly some people who react to porcine and bovine insulin. In the case of bovine insulin there are three amino-acid differences. It is hoped to remove this difference by making human insulin and thus make these people more responsive to therapy.

Mr Owen:

There are possibly two stages in the development of vaccines to combat hepatitis B. The ultimate stage is the complete eradication of the disease. But before that, and until the pool of people who carry the disease has gone, if it ever does, there may well be groups who require special protection. Reference has been made to older people. There are other groups which are particularly exposed to shedding blood. There are those who are operating in artificial-kidney units. In the prison service, prisoners fight and shed blood. Warders are similarly exposed. It also applies in the ambulance service. In schools for the mentally handicapped, children can break windows and cut themselves. We have had cases of hepatitis in these circumstances. Thus, there may well be groups of workers who can benefit from the early development of limited supplies, whereas the final conquest of the disease is much more distant.

Mr Dunican:

After 20 to 30 years research with bacteria we know in great detail how these bacteria work. Yet we never had the tools to apply this knowledge to animal or human systems. The development of recombinant DNA now allows us to look very deeply into how human systems work, to study the targets for various drugs, the targets which may be influenced under stress conditions, how a disease actually works and the auto-immune system. This knowledge will, I think, in the future provide a way of devising new drugs in place of the empirical approach which has hitherto been used. This is one of the major benefits to accrue from RDNA research.

Mr Richards, Rapporteur:

I am grateful to Prof. Dunican for having made that point. Probably the single most important benefit to emerge from this technology is the new ability to analyse normal and abnormal processes in human and animal physiology. There are hopes that we will be able to understand the basic cellular processes and to see how they work both in normal cells and in abnormal cells. It may explain what makes a cell become a tumor, or a cancer cell. We will have a very powerful means of analysing the genetic mechanisms for the synthesis of proteins right down at the molecular level.

TOPIC B: RISKS AND RISKS ASSESSMENT

Mr K. Gibson,
Rapporteur:

Background

Concern was expressed by a group of eminent scientists about genetic recombination because most laboratory work in 1974 used *E. coli,* an organism found in enormous numbers in the human alimentary system. Unease was felt because it was conjectured that, should it prove possible to construct an *E. coli* which had highly pathogenic or carcinogenic properties, or released a hormone or protein in such quantities that created a serious health hazard, then considerable damage could be done to the human population. It should also be noted that the scientists who expressed concern were eminent molecular biologists and were not experts in epidemiology, medical microbiology or population genetics; and had they consulted experts in those fields they would all, without exception, been assured that there was no justification for serious concern. However, once public concern has been expressed, a voluntary temporary pause was agreed by scientists involved in this work whilst government agencies considered the various possibilities and until appropriate guidelines had been drawn up. After considerable debate and advice from scientists, medical and epidemiological experts the general conclusion in 1976 was that, provided suitable precautions were taken, then the benefits far outweighed any risks which may be involved. The laboratory containment precautions are not novel ones or specially designed for this work. They are well established for the routine handling of pathogens in medical and microbiological research.

So What Are the Risks Involved?

As most work has been done and continues to be done in *E. coli*, the comments will be largely restricted to that organism which in certain respects can still be regarded as the *"worst case"* example. It perhaps should also be noted that for pathogenic strains of *E. coli* some 10^8 organisms are usually

required to give a 50/50 chance of causing an infection. In other words, one or a few organisms are not likely to cause an infection.

Possible Escape from a Physical Containment Laboratory

In addition to the generally accepted standards of "*good microbiological practice*" whereby organisms are handled under clean laboratory conditions and a high standard of personal hygiene with restrictions to minimise the possibility of infection of staff there are, in the UK, four levels of containment laboratory, the lowest level is I to the highest containment level IV. The standards and conditions are carefully laid down with general medical and safety surveillance increasing in severity to the highest containment level.

From many years of experience with pathogenic organisms there is well documented evidence to estimate within reasonable limits the risk of escape between the physical containment laboratories. These have been calculated at 10^{-3} between each level. That is, the chances of escape are 1 in 10^3 bacteria. The chances of escape from a category IV laboratory are therefore 1 in 10^{12} bacteria.

Biological Containment

It has also been considered much safer to work with disabled or enfeebled laboratory strains of bacteria which, even if they do escape, would not be able to survive in the environment — at least for any long period of time, and would be extremely unlikely to colonise the human alimentary system.

The usual disabled laboratory strain of *E. coli* used for this work is called K 12. This strain is not usually regarded as pathogenic, and does not usually survive in the human gut for more than 2 or 3 days. It cannot normally compete with the indigenous gut flora and has not been demonstrated to colonise.

During the past four years much work has been done to construct even safer biologically disabled organisms which require special nutrients not normally found in the human gut. There is now, as a result of this work, a very wide range of disabled organisms available suitable for most experimental and large-scale studies.

Three grades of biological disablement have been recognised which depend on the characterisation of the organism — its use with a specified vector system — evidence from animal or human tests to indicate its effectiveness as a disabled system — any special substrate requirements.

Once again a risk factor of 10^{-3} has been assigned to each levels of biological disablement similar to that assigned to the difference between the physical containment level. Therefore, if an approved biologically disabled system is

used then there is a concomitant relaxation of the physical containment conditions required — not only is this considered safer but investigators are encouraged to use them by allowing an appropriate decrease in physical containment.

Risks to Workers

These can be divided into three main groups. Taking the *"worst possible case"* examples, these are:

1. *E. coli* containing a human gene coding for a physiologically active hormone. If, assuming the worst, the normal human gut *E. coli* population were colonised — taken over — by the genetically manipulated organism which expressed the gene continually at the maximum possible rate and, furthermore, that the hormone was totally absorbed by the gut, it has been calculated that, even under these unlikely and extreme conditions, there would be insufficient hormone produced to have any adverse effect on the human.
2. *E. coli* containing a gene coding for a protein which may have antigenic properties. Similarly to (1) if a *"worst case"* example is taken and the gut is colonised by the genetically manipulated organism it is considered most unlikely that sufficient material could be produced to invoke a significant antigenic response.

   The reservation might be in this case of some novel, previously unknown protein material which, although unlikely, may produce some so far unknown effect. However, until such a case arises this must remain speculative, and any likely damage, conjectural.
3. *E. coli* containing a gene coding for a bacterial toxin. If as previously one takes a *"worst case"* example and calculates the maximum quantity of, say, botulinum toxin that could be produced (and this is the most powerful toxin known to man) it is most unlikely that sufficient toxin would be made to cause any adverse effect.

It should be strongly emphasized once again that these are *"worst cases"* and make enormous assumptions which in many cases we know simply do not exist (an example would be that of the hormone insulin, which is only slightly absorbed by the gut. It is largely degraded by enzymes found in the gut).

Risks to the Environment

1. Survival of a Genetically Manipulated Organism in Sewage Systems

Some work has been done in simulated, laboratory model, conditions, and, depending on the nature of the *E. coli* system used, there may be some survival in the sewage system; but for how long and whether it remains viable when put on the land or in the sea must remain, for the present, a matter of guesswork.

2. Deliberate Release of Genetically Manipulated Organisms for, say, Agricultural Purposes

Although no such work has been done to my knowledge, similar arguments would apply as to those put forward concerning the colonisation of the human gut.

It is well established that to maintain a genetically manipulated organism requires carefully controlled conditions, nutrients, antibiotics and other factors; otherwise the *"foreign or inserted gene"* is lost by the host organism. Also the implantation of an additional gene usually weakens the ability of the organism to survive in the highly competitive environment in which organisms usually exist.

It is therefore difficult to envisage a situation, where a genetically manipulated organism will *"take over"* from one normally found in the environment and maintain its inserted gene. Until specific examples become available it is difficult to sensibly argue a case one way or the other, but all the present evidence would indicate that the deliberate or accidental release of a genetically manipulated organism into the environment is unlikely to cause any serious hazard.

3. Effects on the "Gene Pool"

Most genes have been with us for millions of years. Human cells each containing all the known human genes are lost to the environment through natural routes in great numbers each day. There is also some evidence, albeit slender, that some micro-organisms do contain human gene sequences. There does not therefore appear to be any case for concern regarding modification of the natural gene pool by the release of genes into the environment through genetically manipulated organisms.

Industrial Fermentation using Genetically Manipulated Organisms

Since the weight of evidence has indicated that the guidelines concerning laboratory work can be relaxed, the attention of some critics of genetic recombination has focused on industrial applications. Industrial fermentation is strictly the *"use"* of the products of genetic manipulation rather than genetic manipulation *per se*. In general industrial-scale fermentation is considered much safer than laboratory work because industrial fermenters are made of metal and steel pipes are used to supply nutrients etc., compared to the glass vessels and rubber tubing used in laboratory scale work which are more vulnerable to accidental damage.

Industrial fermentation has been well established for many years e.g. in the production of antibiotics, preparation of enzymes and the brewing industry. There is a well recognised very high safety record in the fermentation industry.

In certain cases — such as vaccine production — genetic manipulation offers a much safer alternative for their industrial production. The use of the pathogenic organism is avoided as the appropriate part of the pathogen DNA is inserted into *E. coli* or some other *"relatively"* safe bacterium and this nonpathogenic system is then used in the production of the vaccine.

What are the Remaining Risks as seen after Six Years of Widespread Use of Recombinant DNA Technology?

It should be pointed out that recombinant DNA work is a technique and to date there has been no evidence from the many hundreds of centres throughout the world that it involves any novel biohazard — that is beyond those which are already known to exist with any work involving a microbiological organism.

Therefore, any risks which may exist are due to a hazard already known to be present in the handling of a particular organism i.e. because it is a known pathogen.

In the large-scale use of genetically manipulated organisms the risk of allergic reactions are those which may already exist with the organisms prior to its manipulation.

In Summary

Any risks associated with genetic manipulation still remain conjectural and all the scientific and medical information and data to date has not provided any evidence which suggests that there are any risks associated with this technology beyond those which are already known to exist in work with micro-organisms.

Risk assessment procedures, such as those used in the UK, for the categorisation of work involving genetic recombination have proved flexible, effective and easily operated by local biological safety committees.

The considerable scientific evidence to support this conclusion should not be underestimated. It has provided sufficient evidence to allow national expert advisory groups throughout the world to recommend that the conditions required to undertake work involving genetic recombination can be radically relaxed.

Mr Puglisi,
Rapporteur:

My report is divided into two sections: one deals with the hypothetical risks connected with recombinant DNA technology, which are purely a matter for conjecture, and the second deals with the precautions which can be taken to minimise these risks.

Generally speaking there are two potential sources of risk:
a) the product of an industrial engineering operation and
b) the modified organism that produces it.

The amount of risk associated with a product depends on how industrially pure it is and, in a way, has nothing to do with the risk inherent in recombinant DNA technology itself, i.e. in lab scale technology.

On the other hand the modified organism, i.e. the genetically engineered object which has produced the above-mentioned product, may, theoretically speaking, be associated with a series of conditions which produce phenotypical, genotypical or environmental effects of some relevance, and therefore involving some risk.

The first type of effect arises when the polynucleotide sequences of the chromosome structure become activated, split and discharged. This puts the plant operators at a certain risk and affects the environment, endangering it to an extent which can be calculated according to the reduction in the quantity of the polluting ingredient, its possible integration with the microbial flora of the environment, and the safety regulations and measures in force in the production and waste treatment plants.

In the second effect, the regulative properties of an organism whose polynucleotide sequences have been modified through genetic manipulation may be altered with the possible consequences that its ecological role may also eventually be altered.

Therefore, the level of risk associated with modified organisms depends, once more, on the safety regulations and measures in force in the production and waste treatment plants. My purpose has merely been to describe the genetic risks which may exist, but I am not qualified to assess the exact

amount of risk involved; perhaps a discussion on the subject would be appropriate.

We realise that if someone wished to prepare an organism which contained a toxin able to be transmitted to human beings, he certainly would not ask for anyone's permission, least of all that of the EEC. Nevertheless, let us believe that we live in the best of all possible worlds with Pangloss for President, and I shall make a few remarks concerning possible ways of minimising the risks.

In order to evaluate a risk of precaution, and therefore the definition of the most effective precautions, the goals which may be accomplished by the use of the precaution must first be evaluated. I should just like to mention three very brief points for discussion.

Firstly, reagent cocktails for recombinant DNA technology should only be sold to laboratories and institutes licensed to use them by, for example, the European Laboratory of Molecular Biology in Heidelberg.

Secondly, only products from industrial institutes or laboratories whose competence to carry out such work has been officially recognised by the European Laboratory of Molecular Biology in Heidelberg should be allowed to be put on the market.

Thirdly, scientific magazines should only accept articles referring to recombinant DNA technology if they include in their "*materials and methods*" section the precautions which should be taken to minimize risks.

These are basically criteria for safety bearing in mind the operator, the treatment, waste treatment and the host strains used for genetic engineering. The criteria for using a host strain safely are so well known, that they only deserve a passing mention: if they are temperature-sensitive or dependent strains, i.e. unable to survive outside the controlled temperature conditions of the plant, fermentation jar, pilot plant or industrial plant, etc., there is less risk.

If temperature-sensitive or dependent strains, and strains which have been rendered chemical-dependent by genetically recombining two types of host strain, are used simultaneously, then the strains will have a tenuous hold on life, making it highly improbable that they should misbehave in one of the undesirable ways described earlier.

DISCUSSION

Mr Roskam:

For practical reasons, it is important not to take one single level for conjectural risk and to apply it across the board to all genetic engineering work. An effort should be made to identify work not involving risk and not requiring special safety measures. In my own experience, much of the work is

carried out on defective genes which could not possibly be biologically active. The overall rate of progress on genetic engineering work would be slowed down considerably if unnecessarily strict rules were applied.

Mr Puglisi, Rapporteur:

You have mentioned genes, whose sequencing makes them biologically inactive. However, there are certain sequences which are not functional from a genetic viewpoint, but could still have a vital regulatory effect if they were inserted at a particular point in the DNA sequence of an active organism.

Mr Buringh:

In the Dutch trade union movement, we have up to now always expressed strong reservations about the use of recombinant DNA techniques. Wherever doubt persists, extreme care is needed. Some have said *"There is no proof that it is dangerous"*. For us, the burden of proof should be reversed. The motto should be *"When in doubt, don't"*. In the light of that general position, I would like to ask three questions. Firstly, there has been frequent use of the words *"probable"*, *"improbable"*, and *"highly improbable"*. What can be done to remove the remaining element of doubt. Secondly, what are the risks for a host system other than *E. coli*? Thirdly, what are the risks involved in scaling-up to industrial production?

Mr Stewart:

Despite claims to the contrary, I would like to emphasize that the subject is still controversial. Unlike chemical or radioactive pollution, a new biohazard could proliferate and would therefore be an irreversible event. The burden of proof must therefore be reversed. We must be sure that there are no risks.

In the present state of scientific knowledge, I would also like to go on record as saying that we do not have sufficient knowledge to guarantee that there are no risks. On many issues there is relatively little knowledge. Furthermore, some of the information we have acquired recently indicates that certain risks are greater, not smaller, than we thought five years ago. The specific example relates to virally-caused cancers.

Nor can it be claimed that genetic engineering is safe simply because no accidents have occurred in the six years of its existence. We do not know that there have been no accidents. In the case of radioactivity and chemical carcinogens, serious health hazards were only identified many years later. On the other hand, if it is true that no accident has yet occurred, it may be precisely because strict safety norms have been applied in the laboratory. It is no argument for relaxing precautions now, especially as we are now moving to large-scale work.

Mr Herbig:

The discussion has focused on the prevention of genetically manipulated micro-organisms escaping into the open environment. However, some applications such as the combatting of environmental pollution or nitrogen

fixation in agriculture, will require genetically manipulated organisms which are specifically designed to survive in the natural environment. In view of our relatively limited knowledge of ecological relationships of micro-organisms under controlled laboratory conditions, how can we know what would happen outdoors?

Mr Holt:

It is certainly up to us as scientists to try and allay the fears of the general public. However, I do not believe we could control the sale of components of reactive cocktails. It should be remembered that these enzymes, the components of the reactive cocktail, were discovered in bacteria and exist everywhere in nature. It would be totally impracticable to talk about stopping the sale of these things. They could be easily manufactured in the laboratory.

Mr Bonety:

Dr Gibson referred to the existence of evaluation procedures in the United Kingdom which seemed to be both flexible and effective. Are similar procedures followed in other Member States? Are the public authorities responsible for collecting this information or is it left to the responsibility of the scientific community?

Mr von der Decken:

In Dr Gibson's paper, the chances of escape from a laboratory with the highest level of containment are given at 1 in 10^{12} bacteria. If I understand that correctly, it means that 1 bacterium out of every 10^{12} bacteria handled therein, can ultimately get out. This would seem to set a standard which would then be progressively reduced under industrial conditions. A major incident might occur resulting in a massive release. Could Dr Gibson indicate how possible events of this kind are built into the probability calculations?

It must also be pointed out that every technology, new or old, involves a risk. Even the abandonment of a new technology entails risks. This means our discussion is limited to risk evaluation, i.e.: How great is the risk in relation to the benefits?

Mr Lafontaine:

I can understand the enthusiasm of many of those working on recombinant DNA research. However, we must remain objective. Genetic engineering should not be overrated. There are many other areas where solutions are at least as important, if not more so, in safeguarding the future of mankind. There is a danger of confusing usefulness with necessity, hope with reality. Genetic engineering is certainly a technique which opens the way to progress in research and offers benefits in industry, medicine and pharmaceuticals. But we need to compare the results obtained using RDNA techniques with those of other approaches, tackling the same practical and theoretical problems. Similarly, we must compare the conjectural risks of RDNA with the physical, chemical and biological risks associated with other techniques. I think it is

time to ask the advice of specialists in risk/benefit analysis, such as Rowe in the USA.

Mr Couture:
Is there an internationally recognised body which sets standards for genetic engineering work, like that for radiological protection in the nuclear field?

Mr De Grave:
We have had examples in the past where industry assured us that there were no safety problems. Yet accidents occurred, but there was a tendency to play them down. Contrary to requirements, neither the public nor the health authorities were informed. What steps have been taken to ensure that there are no cover-ups, even of a minor nature, in genetic engineering?

Mr Sapir:
The concept of risk has been looked at from various aspects. Yet there has been no mention of "*social risk*". Quite apart from the type of risk associated with pathogenicity and biohazards, the launching of new types of products on the market could have very significant effects. Secondly, while there was a certain amount of public debate in the United States and other countries at the initial stages, the whole area has more recently become shrouded in a veil of industrial secrecy. Is discussion still possible?

Mr Owen:
There are two steps in relation to risk. These are the same for carcinogenicity and radiation. The first step involves "*risk assessment*" in which a band of probability or a range of options is identified. The second is "*risk acceptance*" where the decision on what to do about it, is taken. Unfortunately, the risk assessment work is often carried out by groups of experts from government and possibly industry, without any wider involvement. A series of options is then presented for risk acceptance by a broader group, often giving rise to arguments about whether the right assessments have been made. We can avoid this problem in the recombinant DNA field by ensuring that all interests are involved in the discussions from the beginning. Many workers' organisations now have scientists of high calibre who can in fact validate or evaluate the probability assessments that have been made.

Mr Busi:
The answers to the question of risk seem to be based more on what is not known, than what is known. In practice, we only know that the risk is extremely small. But no figures have been given as, for example, in the case of radiation. What proportion of total research expenditure on genetic engineering is devoted to the study of risks? I suspect it is extremely small. There is a strong case for creating an international commission whose task would be to inform the public of the real risks associated with the development of the technology.

Mr Zoli:

I would like to ask Mr Puglisi what are the possibilities of "*a looney with a bathtub*" carrying out the type of clandestine activity which he mentioned in his paper?

The Chairman, Mrs Heuser:

Is it not possible to envisage a system for safety research to go hand-in-hand with research on the development of the technology itself?

Mr Gibson, Rapporteur:

To reply to the large number of questions, I would point out firstly that man has been involved in genetic manipulation for a considerable length of time. For example, he has been domesticating animals and harnessing bacteria for fermentation. In the fermentation industry, strain improvement through standard genetic techniques is well established.

Secondly, as Professor Dunican pointed out, considerable information is now available on the genetic structure of micro-organisms, far more so than on the various higher animal forms. In the wake of the so-called recombinant DNA debate, a lot of work has been done in trying to obtain the basic data in relation to "*risk assessment*". We now have considerably more information on which to base our advice.

Thirdly, it must be pointed out that risk assessment work has not been relaxed. It is continuing in the United Kingdom and in the United States. Areas for experiments have been identified. Funds are available and high priority is given to such work. However, the experiments are laborious and there is a feeling among scientists that so much is now known about these micro-organisms, that little more can be achieved in terms of risk assessment.

In the United Kingdom, the Genetic Manipulations Advisory Group (GMAG) has a flexible system for the categorisation of experiments which has much to recommend it. It takes account of all factors including the information already available and local ability to carry out the work.

There were questions about the gathering of information in relation to risk assessment. In the United Kingdom, the GMAG does try to make available as much of this information as possible. It is usually published in the form of notes. At the international level, the European Science Foundation (ESF) distributes information which it receives from the various national bodies.

With regard to what happens in the case of accidents, I cannot comment for the rest of Europe. But within the United Kingdom, all such accidents have to be reported under the Health & Safety at Work Act. There are inspectors to ensure safe conditions and that all information in relation to accidents is noted and made available.

I do not think the patent system impedes public information. In fact, because these are lodged in the Patent Office, they are freely available for inspection by any member of the public.

With regard to worker participation, there has always been consultation with the Trade Union Congress in the United Kingdom. The latter nominates representatives on GMAG. And the newly-constituted Advisory Committee on Dangerous Pathogens (ACDP) in the United Kingdom also has trade union representatives.

Mr Sgaramella:

The conjectural risks associated with RDNA work have been the subject of specific experiments undertaken by the scientific community in response to pressure from public opinion. The risks have been evaluated and, taken as a whole, are considered to be acceptable. The Committee on Genetic Experimentation of the International Council of Scientific Unions (ICSU) has commissioned a detailed study of all available data in relation to risks. It has published a report in accessible language. I was one of its co-signatories. When talking of the continued existence of risk, it is important to first get hold of the material which already exists.

Mr Massue:

How many patents have so far been granted for genetic engineering work worldwide?

Mr Puglisi, Rapporteur:

I certainly don't want to engage in terrorism in a world which already has enough of it. At the same time, I don't believe we live in a utopian world in which botulinial beer was not made.

It must be remembered that industrial processes are vastly more complex than laboratory-type work. It is also questionable whether the bacteria used in a chemical or pharmaceutical industrial process would be the same disabled strains on which our current risk assessments have been calculated.

Then, there is Mr Zoli's question. While it is theoretically possible for an individual or a group to do such work on a home-made basis, the research scale and the investment risk required would be so great that these could only be met either by a great personal commitment or by a major industrial undertaking.

The Chairman, Mrs Heuser:

If it is not possible to do such work at home, then why is it necessary to limit certain material to authorized researchers?

Mr Puglisi, Rapporteur:

Restriction enzymes and reactive cocktails are normally sold to those who have the money to pay for them and thus only go to industry or research institutes. I only wanted to point out that the other possibility existed. If there was a *"looney with a bathtub"*, he would likely to be so eccentric anyway that his behaviour would become conspicuous long before he got round to genetic engineering.

Mr Sgamarella:

In relation to industrial scale-up, it is important to remember that pilot-plants or production plants would be using bacteria designed to produce a specific product. The worst that could happen would be an escape of a certain volume of culture liquid into the environment. But since these bacteria have not undergone natural selection and have been altered to produce a product which is alien to their physiology, they would stand little chance of survival out-of-doors.

Mr Thorley:

Over the last 20 years sophisticated methods of evaluating risk have been developed in the chemical and nuclear industries. The same techniques could be used for the assessment of risk in connection with recombinant DNA.

The disabled strains which are currently used in laboratories for this type of work are, indeed, those which would be used by industry for large-scale industrial work.

Mr Lafontaine:

I am certainly not against the use of the recombinant DNA techniques where their benefits for mankind are clearcut and when the appropriate protection measures are taken to avoid unacceptable risks for man and the environment. At the same time, I can understand that there is a mistrust among the public on the scientific, technical and industrial applications. I would like to propose an approach to the problem similar to that taken towards ionizing radiation and its applications. In the latter instance, measures have been drawn up setting out rules and basic standards. When Euratom was created in 1958, a group of experts (the "*Group of Wise Men*") was set up to propose Directives for the safe use of radiation and nuclear energy. Would it not be reasonable to adopt a similar approach here? The European Communities could in the same way prepare safety standards for use of recombinant DNA.

Mr Gilby:

On behalf of the European Federation of Pharmaceutical Industry Associations (EFPIA), I would like to make several comments. It has been said of the pharmaceutical industry that we have a lot of products in search of a disease. Here, we seem to have an enormous number of safety regulations in search of a hazard.

The use of genetically engineered micro-organisms involves problems no different from those already associated with the large-scale production of antibiotics and which are well understood within the industry. Existing plant processes based on micro-organisms have been specifically designed with full regard for safety. There are well established quality-control procedures for raw materials, intermediates and finished products. The plant is self-contained and regularly monitored to ensure that there is no danger to the outside environment, and no contamination of the process from it.

There are existing processes which use pathogenic organisms for the production of vaccines. The introduction of genetic engineering techniques will present fewer handling risks than at present. For example, the handling of micro-organisms manipulated to produce the protective antigen for foot-and-mouth virus is much ess hazardous than handling the virus itself as at present.

Concern has been expressed about genetically manipulated organisms undergoing some spontaneous change which might lead to contamination of the product or the evolution of a high-risk organism. Research has shown that it is extremely difficult to convert harmless organisms into pathogens. Furthermore, present knowledge shows that the chance of this happening spontaneously are extremely remote.

Mr Buringh:
Up to now, all risk assessment work seems to have been based on *E. coli.* Has there been any risk assessment on other systems, i.e. *B. subtilis* and yeast, especially their long-term effects?

Mr Herbig:
There are applications in agriculture and environmental protection which involve the development of gene-spliced micro-organisms capable of surviving in the natural environment. Who will decide on the release of such organisms? The implications for society would seem to far outreach the responsibility of any individual government or industrial undertaking.

Mr Puglisi, Rapporteur:
With regard, Mr Buringh, to *B. subtilis* and yeast host systems, I don't think there is much to add to the risk assessments based on *E. coli.* The same steps in the approach could be repeated, *mutatis mutandis.*

One should also ask what form accompanying research on risk assessment should take. This can really only be done by an in-depth study of the mechanisms which control the chromosomal sequence. It cannot be done in applied industrial R & D. It must be undertaken in a purely scientific context. On the results obtained, it would then be possible to say whether the genetic engineering technique in question could be used in industry.

Mr Gibson, Rapporteur:
I did mention the use of host systems other than *E. coli*, both in my paper and in subsequent discussion. However, the talk highlighted the "*worst-case*" scenario which involves *E. coli.* Very large numbers exist in the human gut. If such an organism was to become dangerous and pathogenic, then this would be the worst case imaginable. However, there have been experiments with other organisms such as *B. subtilis* and yeast. Results to date indicate that these would be considerably less risky than work with *E. coli.*

The other part of Mr Buringh's question was on possible long-term effects and epidemiological studies. In the United Kingdom, the names of all people

involved in both laboratory and industrial work must be notified to the GMAG and the Health & Safety Executive. Indeed, a long-term epidemiological programme is already envisaged. Nobody sensible would say that, because nothing has happened in six years, nothing will happen in the future. There is a general awareness that, if there are any long-term problems, they have yet to manifest themselves. For this reason, epidemiological monitoring will be undertaken. If there are any problems, these will certainly show up, provided the notification procedure is followed.

Mr Herbig's question on the release of genetically-manipulated organisms into the environment is a difficult one. I have no ready answer. The long-term environmental problems would have to be looked at closely. For instance, in the United Kingdom, the deliberate release of a gene-spliced organism for use in agriculture would have to be examined very carefully by the Ministry of Agriculture, Fisheries and Food before any such release could ever take place.

To summarize, one should firstly not underestimate the amount of work which has been done to try and produce answers to the question of risk assessment. There is now considerable published scientific evidence. The work has been fully supported by the various national bodies. The NIH have implemented an extensive research programme. The results of its risk assessment experiments have been published and are widely available.

Secondly, with regard to industrial applications, one should not overlook the amount of R & D which has to be done before the techniques reach industrial scale. Careful experiments have to be done on the stability of the organism and its pathogenicity. The pharmaceutical and fermentation industries have a well-established safety record in this field. In most European countries, there is legislation governing health and safety at work. Furthermore, any new product must be carefully reviewed by the different ministries concerned and bodies such as the Committee on Safety of Medicines in the United Kingdom, before it can be launched on the market.

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TOPIC C: SAFETY MEASURES

Mr Bruce,
Rapporteur:

The development and possibilities, together with the risks incurred in genetic engineering, have been reviewed in the earlier sections of this colloquy. The risk assessment associated with the work has a direct bearing on the safety measures required to ensure a minimal opportunity for any escape of dangerous material.

Thus the use of a crippled host such as certain strains of *E. coli* K12, which are incapable of surviving outside of the artificial environment created for them within the laboratory, appears to afford absolute protection. Unfortunately nothing in biology should be accepted as being absolute. The strains of *E. coli* K12 have been studied for over 50 years and more is probably known about them than of any other organism.

The DNA material inserted into *E. coli* K12 host cells is usually incorporated into non-mobilisable plasmids as the cloning vector. Should *E. coli* K12 organisms, carrying DNA material in such a non-mobilisable vector, gain access to the human gut it will not be capable of reproducing but there are remote possibilities of mobilisation and transfer of the normally non-mobilisable plasmid vector, by conjugation, to wild strains of *E. coli* resident in the bowel of humans.

The probability of this occurring is very low and can be estimated at 10^{-16} per surviving bacterium per day in the gut. Survival in the gut by *E. coli* K12 is limited on average to 3 days.

Some workers believe that there is a possibility of transfer of genetic material within the flora of the digestive tract to other indigenous bacterial species by methods not reproducible in laboratory experiments.

The probability of any of these conditions is extremely unlikely. So what safety measures can and should be applied to further reduce any chance of a mishap.

It must be borne in mind that safety measures tend to be restrictive on the operator, making his work more laborious and time consuming. The cost of an experiment will also escalate progressively as the safety measures are increased.

It has been implied that the scale-up to industrial production would involve much higher levels of risk. From personal experience, I can give one example where this would not be the case. In my own institute, I am responsible not only for virus containment, mainly foot-and-mouth virus, but also for the only commercial unit in Britain producing foot-and-mouth virus vaccines. In it, we have at any one time thousands of litres of active foot-and-mouth virus culture in tank systems. I regard this as one of the safest aspects of our work. The changeover to a genetically-manipulated vaccine production system would, in my mind, introduce even greater safety.

Take the worst possible accident where an explosion breaks open vessels and blows out windows, with the loss of negative air pressure. A high-concentration aerosol cloud would emanate which would only require the right weather conditions to create a serious foot-and-mouth outbreak, possibly involving several strains.

The aim of genetic engineering work is to remove a small part of the virus genome. This can already be done and purified on a very small scale. This section of the genome would then code for the antigenic abilities associated with the outer surface of the virus particle. It could then be inserted in plasmids and produced in culture from there on. No matter what then happened to the culture, a foot-and-mouth outbreak could not occur. The particles used in the vaccine would be non-infectious to the animals susceptible to foot-and-mouth. The same safety considerations would apply in the case of vaccines against human pathogens.

Within the microbiological disciplines dealing with pathogenic organisms of man and animals, over many years the concepts of good microbiological practice have developed. The last twenty years especially has seen great advances in the principles and practice of laboratory safety.

Good microbiological practice has enabled scientists to manipulate pathogens safely. In the field of genetic manipulation many of the scientists have not experienced in their earlier training the need to use safe laboratory techniques as have scientists in pathology and bacteriology. With the increased awareness of the possible dangers, most have acquired the necessary knowledge and experience. It is most important that training in microbiological safety proceeds steadily with new staff. Advanced training is required for experienced staff in order to cope effectively with the increased levels of containment and the more sophisticated equipment required at the higher levels.

The operational control of safety in a genetic manipulation laboratory should be under the control of a Microbiological Safety Officer. He should be experienced in good microbiological practice and in the operation, maintenance and testing of the safety equipment required. Too often, microbiological safety cabinets and other equipment are put into the laboratory and are accepted as giving a high level of safety without any *in situ* testing. Cabinets need to be installed in the correct location and the seals checked on installation, and regularly thereafter. If the equipment is properly used, it can provide a high level of safety.

A Safety Committee should be established to assist him. An active, knowledgeable committee which is fully informed of the projected experimental work can plan and control the safety protocols of a laboratory conducting work at the Category I and II levels of risk. Some countries (UK and USA) have now delegated control from the Central Authority to these committees, only requiring notification of the experiments at these levels. The higher levels of risk assigned to Category III and IV require much more detailed consideration of assessment of their category and of the containment facility. At these higher levels it is most important that there exist efficient testing systems to establish the integrity of equipment such as microbiological safety cabinets, autoclaves and laboratory ventilation systems. Monitoring of the important physical parameters and the raising of alarms, in the event of failure, is necessary. Plans must be evolved to cope with emergencies which may occur in the event of equipment failure or of accidents.

Because of the complexity of the measures and the higher standards required it is sensible that an experienced national staff should oversee such work conducted at Category III and Category IV levels.

DISCUSSION

Mr Balducci:

As a virologist, I basically agree with what Mr Bruce has said. In 25 years personal experience in diagnostic work on virus diseases, I have cultivated nearly every human virus, both pathogenic and non-pathogenic. In that time we have never picked up an infection from the material on which we were working. Physical containment offers sufficient protection. We have also found that strains grown in tissue culture are significantly weaker than those which we normally find on a bus or in the theatre, and occasionally pick up. However, in undertaking work on a new strain, we have sometimes noticed that the specific antibodies appear in our blood. This could mean that it is possible in some cases that laboratory workers are affected by the material with which they are working. It is a very rare event. Nevertheless we cannot exclude the possibility that an infection could develop and that this infection could be transmitted from one person to another. This militates strongly in favour of introducing genetic engineering techniques.

While I am convinced that the physical containment and biological containment procedures we have devised are sufficient to reduce risk to almost zero, I would favour the creation of a third level of containment, namely: immunological containment. It would leave public opinion with an easier mind. There should also be an integrated world-wide system of surveillance, as already exists in the case of influenza. In nearly all of the larger countries there are specialized laboratories capable of identifying any epidemiological risk. The information would be forwarded to bodies such as the WHO or the *World Influenza Centre*(1) in London. The information would make it possible to develop appropriate vaccines in time. These would be of universal benefit.

Mr Stewart:

I would like to reiterate what was said by Mr Owen this morning on the importance of including representatives of the different social groups in discussions on safety measures. We could all benefit from the experience of the GMAG Committee in the United Kingdom, which is one of the relatively few controlling committees which includes representatives from trade unions and other groups. It is no coincidence that adequate records are kept in Britain, to allow for long-term epidemiological analysis. There are few countries where this is done so systematically. It is not done in France. The GMAG model could be usefully extended to other countries.

It is also important to remember that, ultimately, pollution knows no frontiers. If there ever was an accident, it would be an international event. Safety measures will only make sense, therefore, if they are homogeneous from one country to another. Different safety standards would furthermore create distorsions of competition in favour of countries with more lax safety regulations. The competitive pressures in genetic engineering are intense. Time is critical. Work would quickly move away from countries following more prudent safety regulations. I hope we can reach sufficient agreement here to make some proposals for a homogeneous mechanism of control.

The Chairman, Mrs Heuser:

I must stress once again that it is not the task of this meeting to arrive at common decisions. Nevertheless, your question is of particular importance. I would perhaps ask the Rapporteur to give us some information on comparative safety measures in the different Member States and the United States.

Mr Bonety:

At the outset, I would like to say how much I appreciated Mr Bruce's report. It is worth recalling that the Economic and Social Committee did not

(1) WHO Collaborating Centre for Reference and Research on Influenza, c/o National Institute for Medical Research.

wait to hold a Colloquy before coming out in favour of a European Community Directive in this field. I endorse Mr Bruce's suggestions on the appointment of a safety officer. Some shrugged their shoulders at the idea of a public official doing this job. But if the official is properly trained in the laboratory and in industry, I do not see that it matters whether he is an official or not. In the coalmining industry, one of the first trade union demands was for workers to have their own safety officers. This could not prevent some of the major accidents. But it recognised the right of miners to have a say in their own safety. In view of the international character of the problem, does the Rapporteur agree that there should be uniform safety standards at least at European level?

Some years ago the Economic and Social Committee unanimously called for a Community nuclear safety code. It has not yet been accepted by all the Members States. Is there a danger of divergent safety standards emerging in the DNA field? Could the scientific community not put sufficient moral pressure on national governments and European Commission to look beyond national frontiers and to adopt identical guidelines valid for all Member States.

Mr von der Decken:

Mr Bruce has, to my mind, quite correctly stressed the need for good microbiological practice, the training of new staff and further training. But in a sector which is undergoing such rapid expansion is it possible to maintain standards at this high level?

The United Kingdom is currently working at a high level, and at standards which all other countries should ultimately aim at. However, although the technical possibilities for such protection already exist, I wonder whether the system would operate effectively throughout Europe.

Mr Herbig:

Since we are fortunate to have the chairmen of the different national committees present, I would like to ask them: how many projects are currently running in each country.

Secondly, is there not a danger of a fall in the level of good medical microbiological practice? Standards might fall because safety regulations were being relaxed and also because of the sudden recruitment of a large number of research workers who had no special training in this area.

Mr van Campen:

Listening to some of the earlier questions in this morning's debate I had the impression that no attention was being paid to safety. Mr Bruce's paper and the more recent discussion indicate that much has been done in this field in recent years. I am not so worried about future safety in this field. But it is desirable that we should bring national measures into line within a somewhat broader European framework.

In hospitals in the Netherlands we have a system for the recording of "*false or near accidents*". Would there be a case for recording similar incidents in RDNA laboratories. Information would then be exchanged from which other laboratories could usefully learn.

Mr Fiers:

In 1976, the European Science Foundation set up a liaison committee to coördinate safety measures in Europe. The British GMAG system looked particularly impressive at that time and it was suggested that this should be taken as the model. This turned out to be difficult in practice. The GMAG approach was based on a case-by-case system which operated well in Britain but which could not easily be applied to other countries. There was then a shift in thinking, at least in several European countries, towards following the American guidelines of the National Institutes of Health (NIH). These are very comprehensive and specify in great detail the type of biological and physical containment which should be followed for each experiment. The question was asked: how much difference is there between the guidelines followed by the different European countries. Here again the question was examined by the ESF Liaison Committee which watched how the guidelines were evolving over the years. Considerable research was also done by a committee of the European Molecular Biology Organization (EMBO). Detailed comparison of the guidelines in the principal European countries are set out in its annual reports. This comparative work became progressively less important since there was an overall tendency of convergence towards the NIH model, which some countries followed faithfully.

In the field of risk assessment, I feel there is a confusion, conscious or unconscious, between fundamental R & D and applied work relating to industrial scale-up. RDNA techniques have become so widespread in the laboratory that it is now practically impossible to do any basic biological research without them. The fact that these techniques are now applied on a large scale is no reason for assuming that researchers are particularly inexperienced. Most laboratory workers know what they are doing. Ultimately they are responsible for their own work. Although most of this activity now falls outside the "*guidelines*", it is undertaken within them wherever necessary. Imposing limitations on this type of research would have repercussions not only on the health and well-being of mankind. It would also impede the pursuit of new knowledge, which is the primary aim of scientific research.

Industrial scale-up is an entirely different question. Here, it is being handled by people who no longer have a full grasp of the basic aspects of the system. But, on the other hand, they are now, by definition, working with organisms whose make-up is fully known. Accordingly, it is possible to make a genuine risk assessment of the ability of the organism to survive in different environments.

Fundamental research works with unknowns. Industrial applications relate to known organisms.

Mr Roskam:
Mr Bruce describes elaborate safety measures for the handling of infectious viruses. Should these norms be applied to all genetic engineering experiments?

Mr Bruce, Rapporteur:
I did not wish to give the impression that I wanted the highest standards applied to all experiments. This must largely be associated with the risk assessment. If the risk is considered extremely low, then we are coming into an area where good microbiological practice alone should be sufficient. As the risk becomes greater, the standards of containment must be raised accordingly. In the example of foot-and-mouth vaccines, if we could get the DNA copy of the RNA virus segment which is associated with the antigen production free from all infectivity or pathogenicity, then we would have a means for vaccine production which could be carried out virtually anywhere in the world.

Mr Sgaramella
Many reasonable suggestions have been made covering issues such as immunological monitoring, public involvement and the European harmonisation of safety measures. At the same time, we must not forget that these issues have been discussed in great depth in the United States with wide-scale public involvement. The local community discussed the construction of the Harvard laboratory for months. Similar discussions took place in San Diego, California, and Ann Arbor, Michigan. In discussing the European situation, we should take advantage of the American experience. Their conclusions are set out in the NIH Guidelines. These rules have just been scaled-down as a reasoned and appropriate response to assessments which show the risk to be less significant. When we talk of harmonizing European rules, these should correspond to those currently followed in the United States, not to mention other countries such as Japan or the Soviet Union. If, in 1981, we were to adopt a set of rules which was valid in 1975, we would find ourselves in a disadvantageous and ridiculous position.

Mr Dunican:
In 1976, the European Science Foundation set up a Liaison Committee to see if they could harmonize the different national regulations. It comprised the heads of the various national committees. Its membership was much wider than the EEC, involving some 19 countries, with the United States and Canada as observers.

The Liaison Committee acted as a centre for the collection, comparison and dissemination of information on what the various countries were doing. Earlier this year the ESF Liaison Committee issued a public statement. It

recognised that basically similar guidelines had been introduced in most countries, although some countries were still evolving towards a position already reached by others. It went on to point out that there was unanimous agreement that recombinant DNA work *per se* entailed no significant novel biohazards. It reaffirmed its opinion that there was no need for new legislation for DNA.

Finally, as a mark of confidence in the lack of risk associated with recombinant DNA work, the ESF Committee disbanded itself. However, contact has been maintained between the chairmen in the various countries so as to exchange information. It would be useful to have this statement circulated to the meeting.

The Chairman, Mrs Heuser:

We have now come to an area which is of great importance to us within the Economic and Social Committee. Whatever model of safety guidelines is followed, how binding should such a system be? It would be useful to have further views on this. Specifically, I would like to put the question to Dr Gartland: How satisfactorily has United States' experience been with scale-down and decentralisation?

Mr Gartland:

When the National Institutes of Health issued the first Guidelines in 1976, we specified four levels of physical containment and three levels of biological containment. We had a categorization of different classes of experiments which fell into different levels of combinations of physical and biological containment. At the beginning, we had a rather elaborate system for the registration and review of experiments. We had a requirement for the establishment of institutional biosafety committees. All recombinant DNA work, including work that is now exempted from the Guidelines, had to be reviewed by these biosafety committees. In addition, the registration documents had to be centrally filed with the National Institutes of Health where they underwent a second-level review.

Since 1976, a number of things have happened. Based on risk assessment, there was a feeling that the original Guidelines were too stringent in their containment levels. There was a consensus that the procedures involving the dual-level review, locally and at the NIH, were too cumbersome. It was felt that we needed more flexibility in order to be able to respond to new scientific information. Accordingly, in 1978 there was a major revision of the Guidelines. These lowered containment levels made the procedures more flexible. In 1978, we essentially delegated the registration of all work on *E. coli* systems to the local committees. These registration documents are therefore no longer sent to the NIH.

In 1980, we took the position that all experiments, for which containment levels are specified in the Guidelines, not just *E. coli*, need no longer be

registered with the NIH because the containment levels were pretty straightforward. The local committees, as far as we could determine, were doing a very good job in interpreting the Guidelines. We have not had too many problems with the system and consequently I think the experience has been very good.

Mrs Lund:

In Denmark, we have had a problem in evaluating safety levels for the use of gene-spliced organisms as a means of production or as a tool for research not connected with recombinant DNA. How would Mr Bruce set safety levels in such instances?

Mr Buringh:

I missed reference in Mr Bruce's paper to the drawing up of safety measures required for industrial applications. There is an enormous difference in approach between production workers in a large-scale undertaking and researchers in a laboratory.

I believe it is very necessary to adopt a European Directive, especially in view of the possible transnational implications of risks and the possible distorsions in competition. Why has the draft Community Directive been put in cold storage?

Mr Sapir:

Genetic engineering is being undertaken by an ever larger number of groups. In contrast to laboratories which have long standing experience and high safety standards, work is now being carried out by those who have no particular qualifications in the recombinant DNA field. There are examples of this in Belgium involving subsidiaries of multinational companies in the agri-food sector. There are no rules or committees monitoring this work.

Experience over the last 150 years shows that binding regulations are the only way to ensure that safety standards are applied in a competitive industrial environment. It is the only way to ensure that the safety standards will be respected across the whole range of industrial sectors involved.

Mr Stewart:

In contrast to the United States, our experience in France with voluntary regulations and decentralized control has been rather negative. We have had a number of specific instances where the classification of experiments has not been properly respected. Norms about movements in and out of recombinant DNA laboratories have not been adhered to. It is not sufficient to have a local safety committee, if this committee has no point of reference and no recourse in instances where its recommendations are ignored. We would all no doubt prefer a voluntary and decentralized system which would be much more flexible. Unfortunately, our experience in France has shown that it does not work.

Mr Fiers:

My experience in Belgium with voluntary controls has not been at all negative. In reply to a circular, only one industrial group indicated its intention to do genetic engineering work. Its experiments are accordingly registered. While I cannot be certain, I do not believe that other work is being done under cover. Genetic engineering is not something one can set up at home in the back kitchen. Scientific staff need to be trained and are therefore likely to be known by their colleagues.

Mr Van Hoeck:

Several speakers, including Mr Buringh, have put questions to the Commission concerning activity within the European Community. Taking the word "*rules*" in a very broad sense, the positions in the different Member States are not identical, but nevertheless result in a broadly comparable level of safety in the work being done.

In 1978, the Commission put forward a draft Directive which contained a single definition for work and materials relating to recombinant DNA techniques. It provided for compulsory registration both for public and private bodies and proposed that prior authorisation should be obtained from the national authorities before undertaking the work.

But the state of scientific knowledge has evolved since 1978. The Commission took part in the work of the ESF Liaison Committee which reviewed the situation in the different European countries as well as the United States and Canada. The conclusions, which were summarized by Prof. Dunican, have been circulated to you. These indicate that, for practical purposes, a sufficient degree of harmonisation exists and that this is satisfactory from a safety viewpoint.

This led us to alter the original draft Directive, which had not really been discussed by the Council of Ministers nor formally adopted, into a draft Recommendation. A Directive has the force of law and is binding on Member States who then have to adapt their legislation to the Community Directive. A Recommendation, on the other hand, simply sets out guidelines for the Member States and asks them to take these into account. This draft Recommendation still requests the adoption of a single definition for DNA work. It suggests that the Member States should make notification of all work obligatory, and that all requests for a notification and other documents should be kept for a sufficiently long period so that, in the event of an accident, the origin could be traced. The draft Recommendation was forwarded to the Council in 1980 and has not yet been adopted by the Council.

The Commission also drew up an R & D programme on biomolecular engineering in 1980. One of the research projects deals with methods for detecting possible contamination which could occur in industrial production. The programme is still under discussion by the Council of Ministers.

Mr Zoli:
I do not share the views of those who favour voluntary controls. The issue is of such importance that it should not be left in the hands of the private industry. I would therefore like to ask the European Commission to push ahead with the adoption of a directive so as to provide better safeguards for society.

The Chairman, Mrs Heuser:
Before closing the discussion, I would like to ask the national representatives if they could provide an estimate of the number of experiments currently being undertaken in each country. The figure for Germany has been estimated at 1,000 projects.

Mr Gibson:
In the United Kingdom we now have something like 80 centres involved in genetic manipulation work. The number of ongoing individual projects is very difficult to estimate. As a guesstimate, there must be around 200 projects going on at any one time.

Mr Winkler:
In the Netherlands, there are about 150 projects running at the moment. These are mostly at the P1 level, with about 10% at the P2 level.

Mrs Lund:
In Denmark, there are something like 50 units working on recombinant DNA, but each unit may have several projects.

Mr Rougeon:
In France, the registration committee has examined about 280 projects since the beginning. Multiplying this by a factor of 2 to take account of multiple projects, and dividing by 2 to allow for projects which have been completed, this would give a figure of about 200 projects running.

Mr Sgaramella:
For Italy, it is not easy to give a figure since there is no official registration. However, there are some 20 to 30 laboratories active in the recombinant DNA field. Multiplying this by a factor of 3 to 5, would give an order-of-magnitude estimate of between 100 and 200 projects.

Most of these are at the P1 level. Only a few are at the P2 or P3 level.

Mr Bruce, Rapporteur:
Mr Balducci suggested the use of a third containment barrier against risks, namely the immunological barrier. This should of course be used wherever possible, especially in the case of known human pathogens. In our work on rabies we make sure that all staff are immunized and that we have a suitable level of antibody before starting any work. There may be problems applying this to a completely unknown entity in genetic manipulation work.

With regard to Mr Stewart's question on the representation of different groupings on local safety committees, all I can say is that we do have representatives from all areas within our own institute committee. This is fairly general policy throughout the United Kingdom. In fact, GMAG recommend a more-or-less standard pattern of distribution of the committee membership.

Mr Stewart also raised the possibility of the local safety committee having its recommendations ignored. In our own Institute, and I think this applies to the United Kingdom in general, if the committee got no response when the recommendation was passed through to the Safety Officer and the Director of the Institute, it would, if it was a question of human safety, have recourse to the Health & Safety Executive. If it involved an animal disease, it would in our case be referred directly to me. And if there was any risk of animal disease outside the Institute, I would be raising strong objections about that myself.

To reply to Mr Bonety, guidelines for genetic manipulation work exist in the United Kingdom and of course in the United States. In the field of general laboratory safety, the WHO is fairly near to producing some safety guidelines for microbiology work. This could provide a basis for more general safety guidelines for laboratories, which would include genetic manipulation laboratories, particularly at the lower levels.

Mr von der Decken wanted to know about the training and recruiting of safety staff. It is quite difficult to find trained staff. It is almost always a case of trying to find the people and to train them specifically for the job. But again, it demands a sense of vocation. Safety staff must, in a sense, be *"born"* and not *"made"*. In the United Kingdom there are training courses for safety officers. These are run under various systems. Some of the polytechnics have courses for institute administrators which also cover safety requirements. Training of junior staff, I think, has got to be done at local level. The WHO safety guidelines for microbiological laboratories will, incidentally, include some quite extensive guidelines on training.

Mr van Campen referred to the monitoring of risks, the notification of accidents and the exchange of information. We have very strict rules on the reporting of accidents. These are even stricter in the case of accidents which include any spillage or release of viruses. We have a staff fully conscious of the risks involved. Undisclosed accidents of this sort causing contamination of which we were unaware, might lead to a virus escaping from our normal control and the restricted areas in which we operate. We therefore get very full information. This type of material is not actually published. But all of our related operators in other countries, and certainly those on the Safety Officer Groups with which we are associated, get the benefit of any experience we may have had in the way of accidents. Reciprocal arrangements also apply.

Mr Fiers mentioned the problem of the people involved in industrial scale-up being unaware of the risks. At the scale-up stage, I do feel that there must be an effort to get the characterized organism classified by suitable innocuity testing. It must be proven as safe, if it is going to be handled in an industrial environment which is even moderately open. I am referring here to a pathogen which has been completely immobilized and made non-hazardous in order to get a vaccine, an antigen which will stimulate antibody production but which has got no other undesirable factors present.

Finally, Mrs Lund. If you are establishing a level of containment for gene-spliced organisms, it must be at least at the level of the original organism involved, until such time as you prove its innocuity.

TOPIC D: HEALTH PROTECTION

Mr Coutinho,
Rapporteur

Introduction

Experiments with recombinant DNA are categorised according to the estimate of their conjectural risks. The higher the category of containment, the smaller the chance that the micro-organisms involved can escape from the laboratory or survive in the environment. Most people now agree that, if the guidelines are observed, the risk of escape and survival is extremely small. But theoretically there will always remain a certain risk if work is done with pathogenic or potentially pathogenic micro-organisms. Therefore the health of persons doing genetic manipulation work, should be monitored, mainly for two reasons. The first reason is the protection of the health of the persons involved. The second reason is that supervision of workers' health gives information about the effectiveness of the containment measures taken. If anyone at all is at risk, it is the investigator.

Health Monitoring

From the medical point of view, the worker's own health can only be at risk if he works with pathogenic micro-organisms. It is therefore difficult to see the need for extra medical care if experiments are done in Risk Group I as defined in the WHO classification system for pathogens proposed in 1979. The experiments with micro-organisms which are not pathogenic to man belong to this Risk Group. Extra medical attention would only seem necessary for recombinant DNA experiments in the Risk Groups II through IV, which cover experiments with pathogenic organisms.

A supervisory medical officer should be appointed, who is responsible for the supervision of the worker's health. But the worker himself shares a great deal of this responsibility. He should be aware of the kind of work he is doing and the potential risks involved. If a person starts getting involved in genetic manipulation work in the Risk Groups II through IV, a medical examination

should be performed. During the examinations some general contra-indications to this type of work, should be borne in mind. The same list can be used as contra-indications for continuing this kind of work. These general contra-indications are:

1. Evidence of immune disorders or impaired immune competence.
2. Treatment with immuno-suppressive drugs.
3. Treatment with antibiotics.

   It is known that antibiotics can change the bacterial flora of the gut. This may facilitate colonisation, even by the crippled *E. coli* K12, especially if the bacterium is resistent to the antibiotic that is used. Therefore, if a person starts using antibiotics he should temporarily stop working in the laboratory, until the course is finished.
4. General contra-indications like physical unsuitability.

   Physical handicaps could make it difficult to perform the experiments according to the safety rules. Pregnancy cannot be considered a general contra-indication. It depends on the micro-organism or gene functions involved. If the micro-organism or gene functions entail a risk to the foetus, work should not be continued.

From time to time, an unexplained illness will occur in one of the workers. If this happens, both the medical officer and the worker himself should keep in mind the possibility of a laboratory infection, especially if a laboratory accident has occurred prior to the illness. A thorough medical examination should be carried out. If a laboratory infection is suspected, appropriate measures should be taken. Apart from the case of an illness, it is difficult to see what can be gained by regular health check-ups. The same holds true for regular serological controls unless there is a special reason for it and an appropriate test to do.

There is no evidence that DNA-recombination experiments involve any long-term health hazards. However, suspicion about this may arise later. Accordingly, it is important that morbidity and mortality data of the workers are available. This does not mean that all these data should be registered by the supervisory medical officer, but they should be accessible. This will make it possible to do a retrospective investigation if necessary.

Investigator as a Link between Laboratory and Environment

The risk of a worker who is doing DNA-recombination experiments becoming ill is thought to be extremely small. Nonetheless, we should think about what happens if an investigator doing this kind of work gets a disease that is caused by the micro-organism he has been working with. The risk for other people in his environment does not depend primarily on the patho-

genicity of the micro-organism involved. Much more important is the way in which this micro-organism can be transmitted to other people. For example yellow fever is caused by a virus belonging to the arbovirus group. Yellow fever is a severe disease with a case fatality of 5%. Yellow fever virus can therefore be called a pathogenic micro-organism. This virus cannot, however, be transmitted from man to man. There is a mosquito that acts as a vector for the virus, and it is by an infected mosquito that man becomes infected. Another example is cholera. Cholera is caused by a bacterium. To get infected one has to swallow a relatively large number of bacteria. Only then can the cholera bacilli colonise the gut and cause illness. The disease is not transmitted from man to man under hygienic circumstances. Spread of this disease occurs via water or food, in which the bacilli can multiply. After this multiplication there are enough micro-organisms to infect people. Here again it is not the pathogenicity of the micro-organisms that is of primary importance, but the route of transmission.

In most DNA-recombination experiments, *E. coli* is used as the host cell for DNA-clones. For these experiments a crippled strain is used that does not colonise the human gut. *E. coli*, the normal strain, lives in the gut.

There do exist certain strains of *E. coli* which are pathogenic for man. They cause gastro-enteritis, with diarrhoea as its main symptom. To get infected with this pathogenic strain of *E. coli*, it is necessary to swallow a large number of micro-organisms. Transmission from man to man does not occur under hygienic circumstances. Food or water have to act as an intermediate. It is the same situation as with the spread of cholera. This means that even if an *E. coli* K 12, used for DNA-recombination experiments, becomes pathogenic and infects an investigator, both highly unlikely events, even then the risk of transmission to other people is extremely small, too small to be of any importance.

For almost a century, work has been done with pathogenic micro-organisms in thousands of laboratories all over the world. In earlier times experiments with highly pathogenic organisms were done under primitive circumstances. Occasionally it has happened that laboratory workers became infected with the micro-organisms they were working with. In a few cases this has resulted in small outbreaks. However, large scale outbreaks in which transmission occurred from the laboratory worker to others around him, have never been recorded.

So, even if an investigator doing DNA-recombination experiments becomes infected with the micro-organism he is working with, the risk that he will transmit this micro-organism to his environment is extremely small.

The possible hazards of the recombinant DNA technology for the investigators and the environment have been overestimated. This does not mean that the guidelines which were drawn up with so much care by different

committees in different countries, can now be simply abolished. It does mean, however, that these guidelines should be implemented in a more sensible way. Safety should be guaranteed for the investigators and the environment, but at the same time the experiments should not be unnecessarily hampered.

DISCUSSION

Mr Herbig:

If a sufficient number of medical specialists, i.e. epidemiologists and medical microbiologists, had been involved in the DNA debate in the 1974-1976 period, would we have had fewer formal regulations?

Mr Coutinho, Rapporteur:

The involvement of medical microbiologists and epidemiologists in the early DNA debate, would not, I think, have changed the outcome. The techniques were new to them too. And understanding takes time.

Mr Sgaramella:

We would be seriously shortsighted if we simply continue to discuss the risks associated with the use of recombinant DNA. Unlike 1974-1975, we now know that new combinations of genes can be achieved using other techniques, including micro-injection and cell fusion. These techniques could produce results which are less predictable and therefore more dangerous than anything that could be obtained through recombinant DNA. Personally, I do not believe that it is necessary to control these with a Directive. The results may turn out to be very positive and the risks perfectly manageable. Yet, it is on these issues that we could have a worthwhile debate. Not on RDNA which, in itself, is just a technique, nothing more.

Mr Herbig:

Looking back over the DNA debate in the United States, there is a lesson to be drawn. When a particular group, using whatever kind of provisions or directives, attempts to regulate itself, it gives rise to public suspicion that there is an attempt to do an internal deal. The involvement of a sufficient number of independent specialists would have led to a freer discussion and greater public confidence.

Mr Williams:

In response to Dr Coutinho's paper, I do not believe that infections with recombinant *E. coli* are the central concern. Taking the example of *E. coli* converted to produce human growth hormone, the fear is not that colonisation of man would produce a urinary tract infection, but that it would produce a giant. However, investigations in recent years have shown that the total conversion of the *E. coli* of the gut into growth hormone producers, would be barely enough to make any alteration to the total amount of human growth hormone produced in the normal body. If the epidemiologists had been more prominent in 1974, then it would have become apparent that it was

very unlikely that *E. coli* would have the qualities, or could be endowed with the qualities, which would enable it to spread in epidemic fashion from person to person.

Mr Stewart:

Although I seem to be a lone voice in the wilderness, I would strongly hold to the view that the lowering of safety norms is not simply a rational response to the acquisition of new scientific knowledge. In the United States in 1977, Roy Curtiss III sent an open letter to Donald Frederickson, Director of the NIH. He set out in detail the arguments which led him personally to believe that the risks had been seriously overestimated back in 1974. The letter was very influential at the time in reducing the safety norms. Yet, since then, a number of detailed technical criticisms have been made of Curtiss' letter. Even Curtiss himself recognized a number of these errors. But no effort has been made to tighten up the safety norms accordingly.

The initial NIH Guidelines were introduced following detailed public debate. But the norms have been dramatically lowered since then without a public investigation of anything like the same quality. The current consensus is purely an internal one within the community of interested scientists and industrialists. When people start saying to each other: *"The risks do not exist"*, it becomes very difficult to maintain a contrary opinion. But as a geneticist, these arguments have not satisfied my scientific judgement.

The Chairman, Mrs Heuser:

Perhaps Dr Coutinho would reply, indicating whether he believes a lowering of safety norms would carry an increased health risk.

Mr Coutinho, Rapporteur:

Changing the guidelines will not, I think, involve greater risks. It only means that these guidelines have to be upheld and applied in a sensible way.

To come back to Mr Williams, I was not only talking about disease. I was also talking about infections. Even if there was such a thing as a cancer gene, and if it is transmitted from man to man, then you need an infection to transmit it.

Mr Sgaramella:

I would like to point out to Mr Stewart that all the results of recent risk assessment work done in the United Kingdom, by the NIH, and by EMBO in Heidelberg have been given wide publicity and are available to anyone who cares to read them.

Mr Dunican:

We have seen that there is a fair degree of harmony between the voluntary guidelines for recombinant DNA work operating in the European countries. But in a number of countries, the cultivation of pathogens in laboratories is not covered at all. This is an ironic situation which we should keep in mind.

Secondly, it is frequently suggested that, when dealing with real pathogens, serum samples be kept. I am not a medical person, but I am not quite sure of the value of the procedure, the medical supervision required, and what one does with the serum samples after a period of time. Perhaps they could be useful for long-term epidemiological studies.

Finally, it was suggested that the medical histories of laboratory workers should be made available in case of necessity. Medical histories are private and personal. They should be made available to the medical supervisor or someone like that. They should not be generally available.

Mr Fiers:
It cannot be accepted that the relaxation of the NIH Guidelines was decided internally by the scientific community. It came about as a result of a special conference attended by both American and European virologists. Criticism was invited from all sides. The ensuing relaxation of the Guidelines was based on detailed evaluation. The proceedings of the Conference were published.

Mr Buringh:
There is indeed a requirement for norms to cover work with pathogens. It should be included in a European Community measure.

In addition to the microbiological aspects, attention should be given to the new types of product which will be launched on the market as a result of recombinant DNA techniques. As the number of these products is likely to grow rapidly, there is a need to look at their toxicity, etc.

Mr Busi:
From the discussion, it would appear that the relaxation of the United States Guidelines has been based more on what has not happened rather than on any concrete results of risk evaluation research. Accordingly, I would again put the question: what proportion of the total R & D effort, in terms of money and manhours, is devoted specifically to risk assessment?

Mr Coutinho, Rapporteur:
I agree that the medical histories of individual patients should not be made generally available. But they should be accessible. The supervising Medical Officer should not register these data himself but he should know the name of the general practitioner of the person involved, so that the information can be obtained, if there is a suspicion of a certain risk.

I agree that it is strange that there are no explicit guidelines for work with pathogens. I work in such a laboratory every day. There are no real guidelines, recommended or enforced, as there are for recombinant DNA. I think it would be a good idea to have them.

Mr Koch:

It is interesting to note that the World Health Organization is in the final stages of issuing guidelines for work with pathogenic micro-organisms. With the same aim the Howie report has been published in the United Kingdom. In the Federal Republic of Germany, a code of good laboratory practice in the microbiology laboratory will be published shortly. All these have come about as a direct spin-off of the safety debate on genetic engineering. To this extent, the debate has been a necessary and in the end very fruitful exercise. Genetic engineering itself should only be regarded as one aspect of work with micro-organisms and should not be stigmatised by being the only area with guidelines.

Mrs Lund:

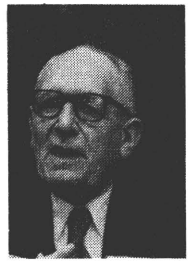
In Denmark, we are against having over-rigid rules. Precisely for safety reasons. You can have elaborate biological containment systems and all sorts of fancy equipment, but it can be counterproductive if not properly used and understood. The main need is for good microbiological practice. We have found that a better safety atmosphere can be created on a voluntary basis. By visiting the laboratories and discussing individual problems and solutions you create an awareness which gives a much higher level of safety than by having strict formal rules.

Mr Nuesch:

As a representative of a small third country, I would like to back up this view. In Switzerland, we have accepted the American Guidelines since 1976. All work is registered annually on a voluntary basis. We have also taken the view from the outset that the safety aspects would probably be covered by our Epidemics Law which is valid for the whole country. We have also tried to organize courses on good microbiological practice on an ongoing basis through the Swiss Society for Microbiology. We feel that a pragmatic approach based on a clear policy has a lot to offer.

TOPIC E: ETHICS

Mr Schumann,
Rapporteur



In honouring me today with an invitation to your colloquy, I do not know whether you are doing so because, as the minister in charge of scientific research in my country many years ago now, I played some part in setting up the European Molecular Biology Organisation EMBO, or because, many years later, I called one of the chapters in my book "*Anguish and Certainty*" on the mystery of life "*From the Molecule to the Anti-destiny.*" But whatever the reason, it is to my incompetence in scientific matters that you have appealed.

To justify this deserved reputation of mine, I shall limit my talk to the metaphysical, ethical and political aspects of the DNA issue, the third following on from the first two.

Let us first take the metaphysical aspect.

On 4 November 1946, in the great amphitheatre of the Sorbonne in Paris, André Malraux celebrated the birth of UNESCO with the words: "*We could only base a human attitude on the tragic, because Man does not know where he is going, and on humanism, because he knows what his starting point is.*"

What doctrine, what science was ever more sure than molecular biology about knowing where Man comes from and about not knowing where he is going? But André Malraux lived long enough to see. Twice at least, and both times in my presence. Once when he gave his academy member's sword to an illustrious doctor-writer, Professor Hamburger, and once when he received the Nehru prize in New Delhi, when the author of "*Lazarus*", who had just returned from the borderland between thinking about and actually experiencing death (for he had been very seriously ill) produced a new and profound view on Jean Hamburger's book "*Power and Fragility*", that molecular biology was taking over the next relay stage of history.

But what does this mean exactly? Think of a French historian like Michelet, an English historian like Toynbee, even a historical philosopher like Hegel or

Marx. They all achieved a wide audience because their aim was to make mankind's adventure intelligible. Through them, history ceased to be a revelation of the past and became, more or less confusedly, a way of mapping out the future. As early as the eighteenth century, Condorcet, in a book entitled *"Sketches of a Historical Tableau of the Progress of the Human Spirit"*, wrote: *"if Man managed to predict phenomena whose laws he knows, why would he think it pointless to sketch out a probable scenario for the future of the human species in the light of its past history?"* Today, the interest which the entire western world is showing in biology arises out of the same fascination. If today's biologists, instead of imposing on themselves the same discipline as their predecessors, are probing into the very nature of life itself *"with the caution of the hunter and the delicacy of the surgeon"*, as André Malraux put it, it is because they, in their turn, nurse the ambition of *"assuming the mantle of destiny"*. In the last analysis, the difference between the *"new"* and the *"old"* biology is the same as that between narrative history and the prophetic history of someone like Oswald Spengler, author of *"The Decline of the West"*. A biology which the human species expects to give an account of its adventure is an anti-destiny.

I should like to sum up this first aspect by a sentence which, although a little superficial, does, I hope, crystallise the basic ideas: *"Physics codify the inevitable, biology codifies the possible, and molecular biology is a sort of dialogue between the inevitable and the possible"*.

This dialogue places Man before the problem of his freedom. The time has therefore come for us to move from the metaphysical to our second aspect, the ethical.

Is it possible to talk about molecular determinism in the same way as one talks about historical determinism? To this question France's two most famous molecular biologists, Professor Jacob and Professor Monod, both of whom have been awarded the Nobel Prize, have given two conflicting answers. To begin with, they agree about what they call *"the philosopher's stone"* of biology and the dream of the bacterial cell, which they describe in a language that fully reveals the poetic bent of their thought. These images translate two bold and simple concepts by two words: emergence and teleonomy, the two properties by which living beings are differentiated from non-living objects or systems. Emergence is the aptitude to reproduce structures of growing complexity, the philosopher's stone on which it is based being DNA, an ingredient of chromosomes and the guardian of heredity.

Teleonomy is the synonym which a certain *"objective modesty"* (the expression is that of Professor Monod himself) has substituted for *"adaptation"*. Is this a confession, an observation? The structure of living things would be no different if it had been conceived with an end in view: the survival of the individual and, above all, the survival of the species. These two essential properties of the living cell amount to a strange virtue: fidelity to the real

programme provided for by heredity. *"If there are 26 letters in my alphabet"*, wrote Professor Jacob, *"4 are used to compose the chemical message through which heredity is determined. Mutations result from errors similar to those introduced into a text by a transcriber or printer. If one B among the millions of others is changed into an A, or an A into a B, the word or sentence is made unrecognisable forever although the alphabet itself is not changed"*. Up to this point, and as long as they stick to scientific observation, the pioneers of molecular biology agree with each other completely. But as soon as they approach the limits of their knowledge and are obliged to conjecture, then their views and philosophies all differ. And the point where they separate from each other is the dividing line between nuclear mechanisms and nervous and cerebral mechanisms.

To show what I mean, I shall compare for you the two inaugural addresses of Professor Jacob and Professor Monod to the Collège de France. On 7 May 1965, when Professor Jacob took his seat in the College for the first time, he said: *"We are totally ignorant of the molecular language of the nervous system, the code in which memory is expressed. The geneticist is convinced that there can be no question of the over-rigid language authorised by the nucleic alphabet. No-one could envisage memory without the existence of innumerable relays and highly complex circuits. But are the knowledge of structures and the understanding of mechanisms sufficient to explain such complex processes as thought? Is there any chance of one day expressing in the language of physics and chemistry the interactions which give rise to a thought, a decision or a feeling? There are grounds for not believing so."*

On 3 November 1967, it was Professor Monod's turn to take his seat in the Collège de France, and everything he said was a direct contradiction of the thesis of Professor Jacob as summarised in the passage I have just quoted to you. His point of departure was the discovery of the so-called *"allosteric"* proteins, whose structure is such that *"they can cause links to form between bodies which would have absolutely no chemical affinity for each other if left on their own and between which no exchange of energy would normally be possible"*. *"My faith in the unity of the living world"*, Professor Monod said, *"would be disappointed if this prodigious organ of teleonomic co-ordination, the central nervous system of Man, did not use this molecular means of communication, already discovered by bacteria, which is represented by "allosteric" interactions"*. And he added: *"Let us suppose that this hypothesis is true. Would we then have the right to say that we are acquainted with the ultimate physical support of thought, of conscience, of knowledge, of poetry, of political or religious ideas, of the most noble plans or the most base ambitions? Yes, we would have to say that all that, all these beings which live within us, are in fact contained, inscribed within the geometric deformations of billions of small molecular crystals"*.

All in all, molecular biology may lead to two concepts of heredity:

- Either there are two systems of heredity, the first determined by a chemical message inscribed along the chromosomes, the second free from all form of planning, with its meaning capable of being modified by the effects of experience, the action of the environment, words and writing;
- Or the unity of the living world requires that any specificity of Man's central nervous system, i.e. the realm of ideas and knowledge, be denied and that any transmissible feeling or thought be an autonomous being endowed with the same emergence and the same adaptation as the bacterial cell.

From the confession of Monod himself, this latter view is conjectural and hypothetical. Both must be used to deduce a DNA policy adapted to the road leading from the molecule to the anti-destiny.

This policy (and here we are coming to our last part) must be the subject of two choices, depending on whether it is a question of the foundations of society in general or the attitude of the public authorities towards genetic manipulation.

Let us therefore look first at the foundations of society in general.

It has been too easily forgotten that as soon as it was born, molecular biology was put on trial by Moscow. Remember the controversy, which continued into the gulags, between Michurin and Lysenko, who has rightly been called the *"Rasputin of biology"*. What was at stake in this trial, this controversy which, I repeat, ended in police repression, was whether acquired characteristics could be passed on to future generations. It was Stalin who decided. The doctrine of hereditary transmission offered too many advantages to a dictatorial power for him to think twice about imposing it.

What a temptation, for any dictator, to be able to manufacture docile citizens, robots who would in their turn give birth to other robots!

At the time, DNA had already been isolated. So none of those who were investigating its structure could become or remain Stalinist without disowning their work. For them the crux of the nucleic message was that lessons could not be received from the environment, and that modifications could only take place according to the whims of the *"order of letters"*. Thus from one moment to the next, and in spite of themselves, the pioneers of the new biology became counter-revolutionaries in the Stalinist lexicon.

DNA has been heretical since 1950 because it promises Man a genesis from within. It was this very issue which caused the break between Professor Monod and the Communist Party, with which he sympathised. He was asked to lecture on the quarrel between Michurin and Lysenko. Of course, he concluded that Lysenko's doctrines did not hold water and that it was not possible to abolish Mendelian laws by a sort of political decree; he therefore

decided that Michurin was right. A few days later he received a letter, which he showed to me, in which he was asked to criticise himself and reverse his conclusions so that they concurred with those of Stalin. Naturally he refused, and that caused the break.

Monod accepted all the consequences of this misadventure. According to him, knowledge is not a means, it is an end in itself. Research must not be influenced even by a search for a sovereign good or for the happiness of mankind. But for it to be an end in itself, certain moral, social and political conditions must be fulfilled. He himself listed them in the following terms: *"Scorn for violence and temporal domination, personal freedom and a constant calling into question considered as a duty"*. In other words, the biologist can only make his own adventure intelligible to mankind in a community based on the rejection of all forms of totalitarianism, including ideologies and régimes.

So much for the first of the two points we should deal with in our last part: the foundations of society in general seen through the morality of the biologist.

The second aspect is the attitude of the powers-that-be towards genetic manipulation. Is the policy of a democratic power towards genetic manipulation determined in advance only by the limits defined by Monod? More precisely, is a scientist who is entirely free in his research, who works like Michurin could have worked in his own country if there had been no Lysenko, free from the obligation to ask himself questions, not like Monod on the conditions, but on the *"moral, social and political"* consequences of genetic manipulation?

The problem of conditions has been examined by us through Monod. Now we must turn to the problem of consequences.

It is no accident that the anguish of a Jean Rostand, for example, at the progress of his discipline is like that of an Oppenheimer or an Otto Kahn at the military uses of the atom. There is a book about the internal reflections and the public declarations of atomic physicists at the time of the first successful explosion of an atomic bomb.

These words are quite astonishing, even upsetting. Although these scientists were all atheists or agnostics, their language suddenly became brutally theological. *"We have performed the work of the devil." "God will not permit it." "We are now at the edge of mystery."* etc. The language of the molecular biologist and the chemist at the realisation of the implications of their discovery is much the same as that I have just mentioned. Let us confine ourselves to Jean Rostand who said: *"We are going to learn to change Man before knowing what he is."* And: *"Is Man capable of handling the chemical controls of his fate?"* And finally: *"Will science turn our grandchildren into*

bewildered gods who will have everything explained but will understand nothing?"

Was it the same anguish which on 26 July 1974 led one of the pioneers of genetic engineering, Professor Paul Berg, to call for a moratorium on research? He gave many reasons for doing so. These are not contradictory, they are complementary.

As you are aware, there was no moratorium. On 6 November 1977, biologists succeeded in making a human hormone for the first time, a real brain hormone, from a bacterium. This prestigious feat, the synthetic creation of a brain hormone, which Professor Berg had feared, had succeeded. Man had entrusted his mission to one of the billions of colibacilli which make up our internal flora.

Why? Because bacteria — despite their primitiveness — follow the same genetic code as our chromosomes. What a marvellous body of laws direct the unity of the living world!

But would this somatostatin (that was its name) bring happiness or terror? Would it lead for example to enzymes which would provide sugar for the starving or would it lead to tailor-made human beings, replicas of the chimeras conjured up by the nightmares of the poets?

This was the important question.

I had the privilege of discussing it above the Atlantic with another French Nobel prize winner, Professor Dausset. *"My impression"*, I told him, *"was that our fears were groundless; since the creation of a brain hormone from a collibacillus, developments in science had been more promising, more reassuring than disquieting, at least for a layman like myself. What do you think, Professor? For example we have discovered a growth hormone which can be used to combat dwarfism. Interferon opens up new vistas for the battle against cancer and has been recently tested on human beings"*. Professor Dausset replied: *"Yes, but don't go too fast. Genetic engineering itself will soon be outdated. The moment may come, and it may come soon, when a gene can be introduced into a cell. Then if a gene can be introduced into a sperm cell, there will be a major risk that men will be programmed by men."*

These were the actual words used by Professor Dausset. I wrote them down immediately and I am quoting them publicly for the first time. I was, however, imprudent enough to reply in my supreme ignorance: *"Mankind will not be had so easily, will not let itself be programmed so easily. If however, I am correct, that is exactly what your amazing discovery of HLA (Human Leucocyte Antigen) has just shown.*

White blood cells, just like red blood cells, are carriers of cellular markers; they are the key to human individuality, the biological definition of the individual. Yes, blood groups distinguish men from all others. And, we should add, blood

groups distinguish men from other men. But it is the human brain which distinguishes man from the animals, by the skills which he acquires after his birth.

Now, the brain is not a computer from which man can only retrieve what he puts in. It is a chemical plant where new, unforeseen combinations are being manufactured continually." The dialogue ends here.

This brings us back to the major controversy between Jacob and Monod. Can the language of physics and chemistry ever challenge the sum of the interactions which produce a thought or a feeling?

The triple lesson of our metaphysical, ethical and political survey is clear. The nucleic message starts with the freedom of man, leads to the responsibility of man and never stops. As André Malraux said: *"Thought is something to be conquered, not something to be repeated".*

DISCUSSION

Mr Mouton:

I was once asked by Prof. André Dumas what I, as a biologist, thought of Monod's position on random mutation. I studied the DNA repair functions which are genetically controlled and which determine the outcome of premutational damage. The damage can occur randomly, but not the mutations themselves. I put the question to François Jacob, who replied that it was dealt with in his book *"The Logic of Living"*. I was then able to reply to Prof. Dumas: *"Yes, mutations exist, but they are not random."* At present we know of six different DNA repair systems. These correct not only DNA strand damage, but also improper base pairings resulting from environmental factors affecting the DNA, such as radiation or DNA-insulting chemicals. These could be a basic cause of mutagenesis and evolution. Personally, I agree with Prof. Jacob for scientific reasons.

On behalf of the European Ecumenical Commission for Church and Society, I have already pointed out in a written submission that whenever science advances, endowing Man with new power over himself and his environment, the question arises of whether the ethics of the discoverer will, or can, develop to encompass the new field.

Will society let him act as its conscience, as in his duty — you do not give matches to little children — and grant him the right of veto if his discovery is used for violent, unethical ends? The precedent created by Curie, Einstein, Szilard, Oppenheimer and Teller in respect of atomic fission and then fusion is still a live issue since the present generation of nuclear weapons is capable of destroying the population of the Earth 20 to 80 times over.

Besides the risks inherent in genetic manipulation even for the peaceful, non-violent purposes mentioned in our programme, can we deliberately turn


B.K. CORTINOS
W. BRUCE

a blind eye to its use for violent, not only military but also civil, ends? Forced biological production is already with us (chickens, hormone-fed calves, plant selection carried to extremes with long-term reduction of the "*genetic pool*"). Its justification is efficiency, which is another expression of the law of the strongest. The test-tube baby exists. How long before we have molecular racism?

"*Genetics puts Ethics on the spot*". So much the better. Science demands that we make up our minds: either progress is accompanied by an attitude of modesty, respect for Man and his environment, or we go the way of other civilizations, kill ourselves by our own arrogance, intoxicated by a power which has gone to our heads, mistaking the Tree of Knowledge of Good and Evil for the Tree of Scientific Knowledge.

Mr Winkler:

The misuse of recombinant DNA is mentioned in Rostand's book. It also came up in yesterday's debate. All knowledge and technology can, of course, be misused. However, pathogenic bacteria and viruses have been selected by nature over millions of years. During all that time, they have, through the process of mutation and natural selection, adapted themselves to overcome thousands of unknown defense factors in the host. They have perfected their own agressive characteristics. Although Man has tried to increase the virulence of certain organisms either for noble or ignoble purposes, he has always failed.

Man cannot match what nature has taken so long to achieve. I do not believe that the recombinant DNA technique will produce a new pathogen within the next 25 years. Even if it did, the pathogen would be a costly and complex weapon to use. The aggressor would have to immunize his own people first. The result would be unreliable and dependent on weather conditions. An available pathogen would be much easier to use. The only relevance the recombinant DNA technique could have in this field would be to mask the organism a bit, thus making detection somewhat more difficult.

Mr Buringh:

It is interesting that Mr Schumann, in adopting a metaphysical approach to the ethical issues, should come directly to the question of freedom. This in turn raises the issue of how freedom should be allocated to different individuals and groups. The one word I missed, was "*democracy*". It means involvement in decisions relating to research and production. This aspect features strongly in recombinant DNA discussions in the Netherlands. The issue is not specific to the RDNA field. Two examples show, however, why it is significant here.

The pharmaceutical industry in the Netherlands has linked its insulin production closely with pig abattoirs. Competition from RDNA processes could put these units out of business, with a consequent loss of jobs.

Secondly, RDNA could be used to produce basic industrial chemicals such as propylene oxide. It would use less energy than conventional processes. Shell is interested in this research and is involved in a biotechnology company in the Netherlands, whose shares have doubled in value over the last year.

For the trade union movement, it means that there must be more democratic control. The question is: how can the individual and interest groups win a greater say over the direction of scientific and technological development.

Mr Fiers:

There is almost unanimous agreement in the scientific world that mutations occur at random. In certain DNA sequences, they might be more frequent if they are exposed to ultraviolet radiation. But overall they are random. Because they had to withstand higher ultraviolet radiation levels during the course of evolution, all organisms have built-in repair mechanisms. These are designed to identify and repair any changes in DNA. But the repair is only partial, the proportion depending on the type of damage. This phenomenon, however, in no way contradicts the random nature of mutations.

I fully support the basic thinking in Mr Schumann's excellent introduction. However, I have a number of specific comments. While there is an apparent divergence, there is no fundamental scientific contradiction between Monod and Jacob. The hereditary information which is transferred to offspring, is carried by DNA. On the other hand, changes can come about within the individual through the allosteric proteins. But it must be remembered that these allosteric proteins are themselves coded by DNA. This means that the organism possesses from birth the information to build the allosteric proteins. At the same time, these proteins can be modelled by the individual's upbringing, experience and education, as if it were a kind of plasticine. There is thus no contradiction between the two systems.

Despite the widespread view to the contrary, the moratorium proposed by Paul Berg and his colleagues was not a general one. It was quite specifically aimed at two types of experiment. The first concerned the transfer of antibiotic-resistant markers to other types of organism which did not naturally have them. This is a very logical suggestion and to my knowledge still holds. Secondly, care should be taken with experiments which might transfer genetic information with might, under certain conditions, code for tumor-causing genes. Furthermore, the moratorium would only apply until work assessing the risks of such experiments had been completed. Following the Asilomar debate, at which several of us here were present, this work was carried out. Experiments on worst case scenarios were undertaken partly in Europe, under the guidance of EMBO but more extensively in the United States.

The results of this risk assessment work led, *inter alia*, to the Ann Arbor Conference. Here, nearly all the signatories of Paul Berg's original letter

recanted. They requested that the NIH Guidelines be relaxed, and this later came about.

Finally, I would like to emphasize the importance of the parallel which Mr Schumann has drawn with the Lysenko era in the Soviet Union. It was not simply a question of the suppression of scientists' rights. It also had enormous practical consequences. Because of the support that Lysenko got for his non-scientific methods, an enormous gap opened up in the field of scientific research which is still visible decades later. The shortfall in Soviet food production can be partly ascribed to the lack of high-yielding crop varieties suited to the particular climate. This was caused by the ban on true genetic research on plant strain improvement.

The same situation applies to recombinant DNA. Hepatitis B is particularly widespread in the Third World. It can only be tackled with vaccines developed through RDNA. Malaria is a serious disease affecting between 200 and 600 million people and vaccines can be developed through RDNA techniques. Thus, the decisions which are taken do not just affect fundamental scientific research. They also have enormous consequences for the well-being of mankind.

Mr Puglisi:
Mr Schumann has depicted heredity as a perfect, watertight system. However, while the hereditary message contained in the chromosome is determined by DNA, it may also be influenced by factors such as the environment, growth conditions, antibiotics and certain metals. Secondly, there is the generally accepted claim that the genetic code is universal. Once again, there are certain subcellular organelles such as mitochondria and chloroplasts and probably also certain sections of tissue which have a genetic code which is not the same as the nucleic code. These introduce elements of internal flexibility into the biological system, which do not fit in with the harsh determinism with which Monod concludes his book.

Mr Stewart:
Mr Schumann reminded us of the dangers of Stalinist totalitarianism. That nightmare was depicted in English literature in George Orwell's *"Nineteen eighty-four"*. A book by another English writer, Aldous Huxley's *"Brave New World"*, also appeared around the same time. His prescience is uncanny. Huxley thought it would take a thousand years for his particular nightmare to happen. Now, only fifty years later, we find ourselves developing the entire technological base for that society. Genetic engineering is only one of many technological developments. Yet taking them together, we now possess the entire arsenal of techniques for the biological and psychological control envisaged by Huxley.

There is also widespread unease at present that genetic engineering, and more generally biotechnology, rest in the hands of multinational concerns.

Since the goals of the multinationals do not always correspond with the interests of society, I think we have good reason to be concerned. If we are to avoid Huxley's scenario we must bring greater participation and democracy to the decision-making which governs both the development and application of biotechnology.

Mr Sgaramella:

I think Mr Stewart is making a major error in mixing science-fiction with science. We must not confuse the fantastic scenarios depicted by Huxley and Orwell with a realistic assessment of what is scientifically possible, now and in the years ahead. I am not, however, referring to things which may become possible in the very distant future.

Mr Stewart, in his written submission, referred to biological warfare aimed at specific civilian groups. What does he mean when he talks of a "*criminal chromosome*"? There is no scientific basis for these claims. None whatsoever. This is cultural terrorism. As for the genetic components of schizophrenia, these are very difficult to define and certainly involve more than one gene. Like all other factors affecting human behaviour, it lies completely outside the scope of genetic manipulation. Science-fiction has an important social function. But we should try to keep the discussion on a realistic plane.

Mr Bonety:

I feel I must reply to Mr Sgaramella.

For many years, I have worked in Electricité de France alongside nuclear engineers. What always struck me was their feeling of absolute certainty, their total refusal to question anything. When I was nominated as Rapporteur for the Economic and Social Committee's Study on a Community Nuclear Safety Code I came into a lot of criticism from these colleagues. But I told them: "*The longer there is controversy the better*". When the point of absolute certainty is reached, there is no longer any opportunity to criticize. There is no involvement of the trade unions and non-establishment groupings in the democratic process. Science is then no longer guided in the interests of society. One of the key points underlined by Mr Schumann was the duty of the scientist to constantly maintain a critical approach. Mr Stewart's concerns are therefore perfectly legitimate. The interests of society as a whole can only be safeguarded by a permanent debate between the scientific experts who make proposals and those who will then decide on their application.

His point in relation to multinationals is equally relevant. We are currently looking at this within the Economic and Social Committee. When the decision-making centre lies outside a country's democratic system then the effectiveness of that democracy is reduced, and workers no longer have any influence in industrial situations which are their primary concern.

Mr Herbig:

I would like briefly to intervene in the controversy between Mr Stewart and Mr Sgaramella. It is true that much of the scientific information which is brought into public debate and political discussion is either poorly or wrongly understood. I will give two examples: Firstly, there was the famous *"murder chromosome"* which was *"discovered"* in the United States towards the end of the 1960's and which was quite simply used to discriminate against a specific minority. Individuals with a particular genetic make-up were branded as potential criminals. No reference was made to the scientific basis for such a theory, nor to the social causes of crime. In the second example a leading scientific publication in Germany, *"Die Umschau"*, carried a paper at the end of 1979 by a recognised scientist. The article dealt with the hormone characteristics of young female rats. The author, in all seriousness, managed to conclude from this that there was possible biological evidence to show that women's liberation was impossible!

I mention these two appalling examples of how science can be poorly or wrongly understood, because, with the growing accumulation of hard scientific knowledge on the human genetic make-up, there is a danger that those in positions of power would be tempted to use this information to justify political policies directed against specific social minorities.

Mr von der Decken:

I fully accept Mr Schumann's point that scientists must always adopt a critical approach to their work. That is a fundamental principle in any thinking society. But I must refute Mr Bonety's suggestion that scientists are unthinking and uncritical. It is not true for my scientific colleagues in Germany, nor of those I have met from France. Secondly, we must once again try to get away from the illusion that there is any such thing as a technology with zero-risk. Thirdly, there is certainly a danger that new techniques may be misused or, as Mr Herbig has pointed out, that scientific information may be misinterpreted by the public and wrongly applied. It is not the scientist's role to try and prove that there is no danger. Rather, the risks should be presented fairly and squarely, so that the public can then decide whether the technology should be used or not.

Mr Sapir:

The principle of scientific freedom is always loudly defended, both generally and in this debate. Yet, in the present difficult economic climate, research budgets are being cut. This seriously curtails scientist's *"freedom"*. Furthermore, in the field of biotechnology, the distinction between fundamental research in the universities and applied industrial R & D is now almost totally obscured. Many researchers have left the universities to set up their own companies. The universities themselves are getting involved in industrial work. They are even registering patents. In taking on such contracts, the universities now find themselves bound to industrial secrecy. Finally, the general development of new technologies in energy, microelectronics and

biotechnology, are closely linked to industrial adaptation and social change. They will surely play a key role in our efforts to overcome the present economic crisis. Can biotechnology then be divorced from economic and political considerations. On the contrary, the decisions are too important to be left to a select few. In the light of these factors, is it still realistic to talk of academic freedom?

Mr Zoli:

Mr Schumann, in his eloquent and erudite address has provided an important complement to yesterday's debate. Scientists seem to take offence when so-called *"science-fiction"* issues, such as the *"looney with a bathtub"*, are brought into the debate. It has been claimed that the idea of a terrorist-inspired epidemic is absurd. But then, all war is absurd. Psychological control is absurd. So too is the idea of looking at the chromosomal structure in order to decide whether an unborn child should get the chance to live. All that is *"science-fiction"*. Yet it is not so far-fetched.

There is also the positive side. Biotechnology may help to solve the problems of world food shortages, poverty and energy. It is a tool which can be used for evil, or for good.

But no-one would contest its third characteristic, namely, that it is an instrument of power. This aspect is deeply worrying, especially when we look at recent technological developments. The conquest of space has been a conquest by the superpowers, mainly for political ends. Computer technology is largely in the hands of multinationals. The nuclear field is similarly dominated by governmental interests. What then is going to happen in the case of DNA? Who will decide whether the research results will be made public? Who will decide whether they should be used? That is the central question.

Mr Schumann, Rapporteur:

If we have to take sides in the debate between Jacob and Monod, I think Dr Mouton is quite right in saying that it should be for scientific rather than metaphysical reasons. Jacob made a distinction between the central nervous system and the cellular system, simply for reasons of scientific caution. Monod, on the other hand, wanted so much to believe in the unity of the living world, that he resorted to the allosteric enzymes to go beyond the realm of pure scientific observation. That seems to me the central point. Professor Fiers quite rightly pointed out that the basic scientific work of both men is identical. It is only when they pass from observation to conjecture, that their views diverge.

I am also grateful to Professor Fiers for pointing out that the moratorium proposed by Paul Berg in 1974 was to be limited in scope and in time. As it turned out, there was no moratorium at all.

Professor Winkler referred to the unlikelihood of microbiology leading to the creation of new pathogens. I can only agree. The prospect has worried scientists from time to time. However, I think their central concern was really to know whether man would be able to handle the chemical controls of his own destiny.

Mr Buringh referred to democratic involvement in research. I already quoted Monod's condemnation of all totalitarian regimes and his statement that democratic freedom is an essential precondition for genuine scientific research. Mr Buringh is also right, if he means that the democratic process is one which never ends. The fact that we belong to a small privileged group of nations enjoying democratic freedom does not absolve us of the duty to defend that freedom. An ever larger number of people must have an effective say on issues affecting their future. It cannot be left to a small minority which might be tempted to exploit technological know-how in its own particular commercial interest.

I particularly liked Professor Puglisi's phrase that there are elements of *"flexibility"* in the DNA heredity system. In using it, he implicitly supports Jacob against Monod.

When Mr Stewart referred to George Orwell's *"Nineteen eighty-four"* and Aldous Huxley's *"Brave New World"* he intentionally mixed up the issue of science-fiction with that of the multinationals. They are two quite separate questions.

Science-fiction, here I am also replying to Mr Zoli, has an extremely important social function in that it acts both as a warning and a stimulus. When a genius like Huxley, or a serious humorist like Orwell, describe the world as it might be or as it should not be, they exercise a salutory influence on government. There is also a link with Mr Buringh's call for broader democratic involvement. While the average citizen is not able to follow the development of science at academic level, he can easily read works such as those of Orwell and Huxley. In this way, he can come to grips with science.

Mr Bonety stressed the need for a continual questioning. He recalled the fact that the Economic and Social Committee has proposed a Community Nuclear Safety Code. There is no better area in which this type of democratic control should operate. Between technocrats who may tend to play down problems and science-fiction supporters who may exaggerate them, there is a golden mean. It is here the process of democratic control has an important role.

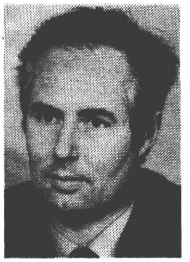
Mr Herbig rightly pointed to the misuse of scientific information and the kind of *"scientific Mc Carthyism"* which emerged in the United States at the end of the 1960's of which the idea of a *"murder chromosome"* was an extreme example.

Professor von der Decken pointed out that there was always a risk. In the recombinant DNA field, the concerns of 1974 have been superseded by the prospect of positive benefits such as human growth hormone or interferon. But we must remember Professor Dausset's remark that genetic engineering itself may soon be outdated. If it one day becomes possible to introduce a gene directly into a cell, the risk that man will be programmed by men will reemerge, without any use being made of recombinant DNA.

I have a particular interest in Mr Sapir's question on research budgets. When I was minister, public R & D expenditure in France reached almost 2% of GNP. It is now under 1%. Admittedly, the economic climate is different and much of the work is now carried out by industry. Yet if science is to progress it must be preserved as an end in itself. This does not mean that the interests of a few privileged researchers should be favoured at the expense of the right of all to benefit. At the same time we must defend pure science in the face of economic pressures which put greater emphasis on applied R & D.

TOPIC F: PUBLIC INFORMATION

Mr Herbig,
Rapporteur:



It should be stated first of all that science and technology do not exist in a vacuum. The controversy about nuclear energy and the problems caused by microelectronics have made a considerable body of the general public aware of the social consequences of scientific and technological discoveries. The implementation of technological discoveries of any significance is increasingly dependent on public discussion and the workings of a more and more democratic decision-making process. Moreover, public criticism and resistance on nuclear issues has revealed shortcomings in official plans on technical matters such as waste disposal and estimates of future needs.

In the case of the new genetic engineering techniques, it was the scientific community itself which first pointed out the possible risks involved in recombining DNA *in vitro*. The voluntary "*moratorium*" of 1974 and the safety guidelines developed afterwards for research were without doubt a laudable first step. But during the ensuing public controversy those involved increasingly tried to block public criticism of self-policing by scientists and counter government measures.

Moreover, focusing on the safety problems of research technology diverted attention in public discussions away from the technical possibilities of applying such technology and the problems involved. In my view, such technical applications in industry, medicine and agriculture will be far more important in the medium and long term than the question of the dangers of infection resulting from genetic research. I feel that it is necessary right now to recognise these possibilities and problems and discuss them, in order to reach socially acceptable decisions concerning policy for research and technology. For today the foundations are being laid for developments which tomorrow will present us with situations which may well appear to be constraints.

Genetic engineering techniques have led to a revolution in the control of natural processes by science and technology. Deliberate intervention in the molecular regulatory processes of the living cell, and indeed of whole

organisms, has proved to be the springboard into a new era of biological technology. But as well as having uses which cannot be disputed, genetic engineering creates a whole host of social and political problems. The most important of these does not arise from the general ambivalence towards technology in itself, which seems almost to be one of the laws of nature, but from an ambivalence about the social goals and interests behind the decisions to be taken about how to put discoveries into effect.

For the first time it will be possible to conduct a systematic investigation of the molecular structure of the human genome. It may be possible to shed some light on the molecular causes of hereditary diseases, diagnose a growing number of such diseases at an early stage and prevent the birth of unhealthy children. But at the same time, there is a danger that the knowledge being acquired about inherent human characteristics will be used not only for medical but also for social purposes.

Past experiences about the social use of biological and genetic data all point to the same conclusion: the demand for genetic labels, with which social problems can be shown to be biological in origin, is great. The *"murder chromosome"*, the inherent intelligence quotient, the sickle cell characteristic, and the case of chemical workers predisposed to cancer are all examples of this. In each case the *"genetic"* label has served as a means for transferring the responsibility for some striking defect or social disadvantage from society or powerful institutions to the individual. The growing availability of such labels will probably lead in the future to a conflict between people's aspirations for social equality and differences diagnosed as genetic in origin. Such a conflict must be decided in favour of social equality.

Genetic therapy should be developed to help cure illnesses which have been clearly identified as being hereditary. But this would be difficult in a multi-factor context, in which not only medical but also social factors had helped bring on an illness.

Binding directives or protective measures should be designed to protect helpless patients from hasty researchers.

Suggestions like those made in West Germany by the well-known scientific journalist von Ditfurth, whereby people would be compensated for alleged genetic defects caused by medical care involving extensive genetic engineering work, are in several ways problematical. Firstly, it has so far not been established that medical and social care does have a dysgenic effect. Secondly, such suggestions ignore the really dysgenic effects on our civilization caused by the multitude of mutagenic and teratogenic substances with which we are in contact every day. Thirdly, they legitimize human genetic engineering on an extensive scale, which again could be strongly determined by social objectives.

It is not disputed that the prospects for genetic engineering in the field of general medicine and pharmacology are highly promising. But the dangers

involved should not be overlooked. The health authorities, the medical profession, the drugs industry and a considerable part of basic biomedical research is mainly concerned with developing cures for illnesses which to an increasing extent are due to environmental factors. The aim is not to prevent illness from occuring but to help people to live with the causes of illnesses.

The extraordinary potential of biomedical progress for innovation through genetic engineering is therefore, in all probability, being developed along the same lines. With the help of increasingly costly medical and pharmacological machinery, people are being tailored to fit into an increasingly hostile social and technical environment. But some sort of counterweight should be created here by laying down clear priorities in the field of publicly financed research. The goal ought to be preventive medicine.

In the western industrialized countries a powerful movement towards concentration is at present taking place in the field of agricultural technology. Multinational chemical and drug groups with interests in agricultural chemicals are engaged in the large scale buying-up of seed-producing firms, which are mainly medium-sized. From now on such groups may be able to offer *"under one roof"* a whole package of modern agricultural technology from seeds to weedkillers and pesticides.

The increasingly complicated technology involved in the molecular and cell biological techniques used in plant breeding will strengthen this movement towards concentration further. A few agricultural multinationals will be developing *"modern"* plant species on a world scale and at the same time selling the chemicals to go with them, which will further aggravate the problems of an agricultural industry which is already extremely unnatural and dependent on chemicals. What is needed are economic and technical developments which lead to greater genetic variety in plants, a partial de-industrialization of methods of cultivation and to less ecologically dubious forms of pest control.

If the industrial countries want to contribute towards solving the nutritional problem in those regions which are regularly hit by famine by manipulating the genetic structure of useful plants or their symbionts, there are lessons to be learnt from the so-called *"Green Revolution"*. The problems cannot be solved by an agricultural sector which is expensive, highly mechanised and dependent on chemicals, as is the case in the industrial countries. In the first place, such an agricultural set-up utilises only a minority of landowners and commercially-oriented big farmers, and not the mass of small farmers. The agricultural technology offered to the Third World by groups from the western industrialized countries is landowner-oriented. There is therefore a need, as far as publicly financed research is concerned, to lay down clear priorities to favour *"low input"* agricultural technology geared to the requirements of small farmers.

In the major industrialized countries there are now systematic links at several levels between basic research in molecular biology on the one hand and public institutions and private firms on the other. These include private initiatives from researchers who market their research findings through private firms, partnerships between public research institutes and commercial firms, and, finally, alliances for specific projects between individual researchers in the university or Max Planck institutes in line with the requirements of the research ministry in Bonn. The aim of such links is to get basic research findings applied rapidly in industry.

But apart from the short-term advantages which they provide for individual researchers, industrial firms or states, such links are highly questionable. The potential for innovation of industry, which is geared to the economic success of private firms, tends, in essential areas, to be diverted away from what is socially and politically desirable. If the aim is to be healthy, then the emphasis should be put on keeping healthy and not on selling medicines. If the aim is improved agricultural technology for famine-stricken areas, then techniques must be developed for people who are too poor to pay for them.

Such opportunities are not taken up by the profit-oriented economy. Needs remain unsatisfied although it would be economically and technically possible to satisfy them. Publicly financed "*free*" research is the only tool in our society which can recognize these needs and come up with solutions for satisfying them. For this reason its independence from economic interests ought to be guaranteed.

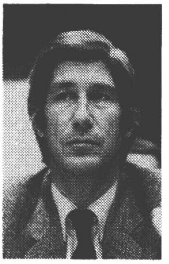
A whole host of leading industrial countries, including the European Community, have initiated investigations into the possibilities of biological research and technology. With the exception of the outstanding (apart from some debatable points) study of Gros, Jacob and Royer entitled "*Sciences de la Vie et Société*" (The Life Sciences and Society) such surveys are obsessed with what is technically feasible. But the real need is to consider the development of biological science and technology from the point of view of social an political necessities, in order to establish reference points for political objectives for practically oriented research and technical development.

DISCUSSION

The Chairman, Mrs Heuser:

I would like both the scientists and those involved in public information to address themselves very specifically to the topic under discussion. What arrangements do we need to facilitate public understanding, to remove mistrust, or alternatively to arouse a questioning attitude, where this is necessary?

Mr de Rosnay:



I recognise the need for a constructive dialogue between scientists and the general public; but the difficulty here is that the public is not a homogenous mass, so any dialogue has to be on several levels: with young people still being trained, with people who wish to know about a new culture resulting from large-scale technology, with the media, with leaders of public life and the industrial world, and with scientists in other disciplines. Such an approach is valid both for genetic engineering and biology in general.

For each of these groups, information must be transmitted differently. To quote Mc Luhan, there are *"media"* and *"messages"*; the latter differ for each social group, which makes communication difficult.

Another important point is that the general public usually receives information in fits and starts, whereas scientific research is a continuous process. In a way the journalist, who is always *"in too much of a hurry"*, and the scientist, who is always considered as being *"too cautious"*, are opposing forces. The media send out *"flashes"* of information which chop the real world of scientific development into slices.

Scientific discovery is then no longer situated in its general context, and the hasty and fragmentary provision of information makes the layman feel afraid, threatened, in danger.

What is more, the most interesting aspects of such discoveries are not mentioned at all. For instance, no-one says that genetic engineering is a powerful tool for basic research thanks to the purification of genes and the study of the expression of such genes. One might also mention the role of gene-synthesising machines (for today it is possible to synthesise 12 nucleotides attached to each other in 6 hours) or protein analysers (40 amino acids in a day, and soon 100 to 150 using only very small quantities of substance).

Once again the newsflash will speak of a *"gene-synthesising machine"* but will not explain its relationship to genetic engineering.

So how are we to put across the idea of continuous progression? Well, we have to provide keys, a compass and a map, and show the significance of a discovery and the meaning of its impact on society.

One new topic which is currently attracting particular interest in university circles is "*Science, Technology and Society*" (STS), which enables one to identify a few broad channels for improving communication between the scientist and the general public.

This process of transfer is based on three factors. Firstly, one must know what one is talking about. This is all to do with mass education. The thing is to help people to understand and find a language which enables others to understand.

Secondly, one must situate an event within its context. One must adopt a systemic approach as a back-up to the analytical approach which has traditionally been the foundation of our education system.

Thirdly, and this aspect is important, the public must be given the means of assessing the implications of these branches of science and technology for society from the individual, social, economic or even philosophical point of view.

Finally, the journalist must learn to project himself into the future, not to alarm people but to describe what might happen. He must therefore not overlook any of the implications of a discovery and paint a picture af what the future might be like.

Projecting oneself into the future is also the means, starting in the present, of regaining the sense of a process and of passing from the discontinuous to the continuous. One can also create a basis for a dialogue between scientists, the public and decision-makers.

Mrs Fuks:

There are several reasons why we have to respond to the preoccupations of public opinion. Two of these have already been mentioned. Firstly, information is needed on technical risks. The second involves the so-called "*social risks*" i.e. the possibility that the technology would be misused by a particular group or government. There is also a third reason. The level of general education in the industrially developed countries is far higher than in the past. There is access to mass media and new information technologies. There is a need to inform but equally a need to take account of the citizen's view. The public must have the feeling of actually being involved in the development of science. Efforts to adopt a new approach in scientific journalism are therefore welcome.

Clearly, the way in which science is organized is changing. In the field of biology, the distinction between fundamental and applied R & D is no longer clear-cut. There is therefore also a need for more information on the decision-making process, from the initial idea to the final application. We should also look at these structures in order to find the most appropriate way of keeping the public properly informed. It is not sufficient merely to provide infor-

mation. Some sense of imagination must also be shown in the institutional field to encourage groups representing the general public to get informed and be involved in decision-making.

Mr von der Decken:

In providing public information, what level of detail is required? Where there is a dialogue, the level is automatically regulated. But this feedback doesn't exist in a straight information process. If the information is too detailed for the current level of knowledge of those for whom it is intended, then the objective of providing greater clarity will certainly not be achieved. If too little information is provided, a climate of mistrust can very easily spring up. Our society is so complex, that it is impossible for an individual, and that includes scientists, to follow technological developments in every field down to the last detail. Together, the public, scientific journalists and scientists have to try and strike the right level.

Mr Mouton:

Scientists themselves have an important role to play in public information. It is not enough for them just to publish the results of their research. They must also be responsible as human beings. We have seen what can happen. Oppenheimer, who invented the A bomb, refused to make the H bomb. Then Teller said he wasn't responsible for the A bomb, so it was all right for him to make the H bomb. Again, the scientists believed that the atomic bomb was to be demonstrated to Japanese observers in a desert. Instead it was dropped on Hiroshima. Scientists are responsible, like the rest of us. They are people with religious beliefs and ethical values. They have the responsibility to bring issues to the attention of the public authorities and the general public.

In providing information to the public, scientists must be able to explain things in simple terms. I fully agree with Mr de Rosnay on this point. His book *"From the Atom to the Cell"* is a good example of how a message can be put across in simple language. There is also a need to teach biology in schools at an earlier stage. It must not simply be descriptive. Children should be able to get a broad understanding of what constitutes life. While the prospect is somewhat frightening, we have now reached the stage where we have to make advances in the ethical side which match our power over nature. If not, we will wipe ourselves out. Other civilizations before us have vanished, though we don't really know why.

Scientists can help by joining discussion groups and also by providing back-up for the scientific journalists. Once they have made a discovery, they should also devote part of their time to public information. It may not prevent knowledge being used for evil purposes, but it will certainly help to create a positive climate of debate.

Mr Stewart:

We have been asked how we can allay public suspicion of new technology. We will never succeed so long as we look on it as a one-way-process from the

scientist, through the journalist, to the public. The public must be able to participate actively and feel that it can get the information required. The technical complexity of the subject, however, creates an immediate difficulty. Here again, the experience of Cambridge, Massachusetts, provides a good example. The citizens on the Cambridge Review Board successfully came to terms with a complex subject, because they had at their disposal experts who disagreed among themselves. Had they been confronted by experts who all said the same thing, they would have been forced to passively accept it. By questioning the different standpoints, confronting the experts and listening to their arguments, they were able to form a genuine independent opinion. As scientists therefore, we should not feel it is a bad thing to have inconclusive debates amongst ourselves. In fact it is our only hope. If we try to promulgate a single truth, using clever mass-media techniques, we will never succeed in gaining public confidence.

The point made by Joël de Rosnay that the public is not a uniform phenomenon is extremely important. He specifically cited the example of industrialists. However, the relationship between scientists and industrialists is not the same as that between scientists and the general public. In the first case, a natural two-way communication exists. In the second, we have to look for a different model. The University of Amsterdam conducted a successful experiment recently in setting up *"Science Shops"*. In this system, the scientists in the university put themselves at the disposal of interest groups such as consumers and trade unions to answer questions they would like investigated. We must develop this kind of active relationship between the scientific community and the public.

Mrs Lund:

Scientists can be criticized for using artificial language and for often talking with great authority in areas which are not really their own. In such circumstances, it is understandable that the public gets confused and fears the worst.

A greater effort should be made to present issues in such a way that there is worthwhile public discussion. It is not a waste of effort for scientists to communicate with the public. Nor does one become a better scientist by hiding behind difficult words.

Mr Herbig, Rapporteur:

The main criticism should not, I think, be levelled at scientific journalists and the media. They are well able to handle technical material and communicate it to the public. Taking a cross-section of the press in Germany and the United States, I would regard that problem as already largely solved.

However, there is still the need, stressed by Mrs Fuks, to make the decision-making process more transparent.

Too often, we hear that genetic engineering will solve the problems of world hunger, health, environment and energy. In the future, we should it make it clear that technological development is a very diverse process. Different social groups will be affected in different ways. It will also be necessary to involve the public in political debate at an earlier stage in the decision-making process. Here scientific journalism can contribute.

CLOSING REMARKS

The Chairman, Mrs Heuser:

We have reached the end of our discussions.

One question seems to remain. How much extra wisdom does information confer? Or, how much more certain am I now, than at the opening of the debate? It is a question which will be long debated.

One thing, however, is evident. It is the burden that freedom entails. It is the burden of having to take responsibility for decisions without guarantees as to their ultimate consequences. It is true for both scientists and politicians. It applies to all of us, and to every field of activity. Man lives in a world, caught, as Mr Schumann put it, between the most noble plans and the basest intentions.

In this morning's debate, it was said that research should be an end in itself and should not be planned in relation to specific applications. I am not in a position here to judge that issue. It is so large, that it would require another colloquy, which might never end.

Much has been said on the relationship between the scientists and the public. It has been claimed that mistrust between the two groups is a healthy phenomenon. But we must also remember that human relations within the community must be based on trust. In that regard, each of us has a responsibility.

APPENDIX

STUDY ON SAFETY MEASURES AGAINST THE CONJUNCTURAL RISKS ASSOCIATED WITH RECOMBINANT DNA WORK

drawn up by the Economic and Social Committee's Section for Protection of the Environment, Public Health and Consumer Affairs,

Brussels, 25 November 1980

Rapporteur: Mrs HEUSER

Object of the Study

In April 1979 the Council asked the Committee for an Opinion on the Proposal for a Council Directive establishing Safety Measures against Conjectural Risks associated with Recombinant DNA Work.

This Opinion was delivered in July 1979([1]). The Committee unanimously endorsed the issuing of a Directive, but had considerable reservations concerning the assessment of the probability, extent and frequency of the suspected hazards.

The Committee also thought that there was as yet too little information on the specific technical and biological safety measures and their effectiveness vis-à-vis the suspected hazards.

In general, the Committee considered the genetic engineering information on which the proposal for a Directive was based to be behind the state of knowledge obtaining at the time the proposal was submitted.

In order to take account of all factors, and neither unduly impede research and utilization nor neglect the protection of Member State citizens, the Committee decided to draw up a Study dealing in particular with the problems set out in points 2.9. and 2.10. of its 1979 Opinion.

On this basis, a hearing was to be held — jointly with the Commission — in order to gather the views of experts from the world of science, health care, farming, industry and the trade unions and of representatives of the public interest.

The Committee started its preparatory work immediately so that the findings of this Study and the hearing could be presented while the decision-making concerning the proposed Directive was still in progress.

During this preliminary work, the Commission's Draft Council Recommendation concerning the Registration of Recombinant DNA (Deoxyribonucleic Acid) Work was drawn up. It was referred to the Committee on 26 September 1980.

Even if many of the suggestions in the ESC Opinion on the Proposal for a Council Directive establishing Safety Measures Against Conjectural Risks Associated with Recombinant DNA Work were taken up in the new recommendations, the present Study has not become superfluous. Genetic engineering methods have raised many questions which are still unanswered. The problems will not be solved merely through a pragmatic

([1]) O.J. No. C 247, 1 October 1979, p. 3.

adaptation of the safety measures or measures concerning the registration of genetic engineering work laid down by the authorities.

The authors of this Study have tried to put across difficult scientific concepts in such a way that they will be comprehensible to the layman, as they consider it essential that the citizens of the Community should have an understanding of this area of research which is so promising but difficult to delimit, with its implications for man and his environment.

Definitions

Recombination of DNA

The coupling of DNA molecules outside a living organism to form a new molecule not occuring in nature and the introduction of this new molecule into a host organism, where it is reproduced and passed on to future generations of the host organism.

1. ***Host organism:*** an organism into which a recombinant DNA is introduced.
2. ***Donor organism:*** an organism whose DNA, or parts thereof, are coupled with the vector and then introduced into the host organism. This DNA can be isolated from the donor or produced synthetically.
3. ***Vectors:*** DNA molecules capable of multiplying (e.g. plasmids, viruses) which are coupled with donor DNA and introduced into the host organism.

Genetic engineering risks

Any work on the production, introduction and reproduction of recombinant DNA, including any work with host organisms containing recombinant DNA.

Genetic Engineering risks

Any special risks which might arise with, or through working with, recombinant DNA or organisms containing recombinant DNA.

Safety measures

Any measures capable of reducing or precluding genetic engineering risks or designed for that purpose.

Historical Background

Modern genetic engineering methods represent an application of modern genetic and enzymological knowledge, gained from quite unrelated processes.

Modern genetics has shown that all genetic information is contained in thread-shaped molecules known as nucleic acids (1944). The discovery of the structure of the nucleic acids (1953) and the deciphering of the code in which genetic information is transferred in DNA (1961-1965) were revolutionary discoveries in modern biology. At the same time, it was learnt how to isolate nucleic acids as functioning molecules and reintroduce them into organisms.

At the same time, modern molecular biology succeeded in discovering many of the enzymes involved in numerous important life processes and the way in which they operated. Thus, enzymes were discovered which propagated nucleic acids, repaired nucleic acids which were damaged and attached broken pieces of DNA together again (1956 and later).

Genetic and biochemical studies led to the isolation of the so-called *"restriction enzymes"*, which cut DNA only in certain places in a predetermined sequence (1965).

With the help of these restriction enzymes, it is possible to cut DNA molecules, which are very long, into specific pieces, separate them from each other and link them up with isolated pieces of DNA of a different origin by using enzymes. Under certain conditions, one can obtain DNA molecules which can operate after re-insertion into another organism, i.e. their genetic information is read by the host organism as if it were its own, utilized and transmitted to succeeding generations.

This practical application of new genetic, biochemical and molecular biological knowledge was neither intentional nor foreseeable. When it was suddenly realized at the beginning of the 1970s what extraordinary possibilities were opening up, scientists and informed members of the public alike were taken by surprise. As a result, genetic engineering was considered by some sectors of popular opinion as a great breakthrough and condemned as a lethal threat by others.

Initial experiments with the new technology and intensive discussions within the world of science and between scientists and members of the public have reduced both expectations and fears to a reasonable level. Genetic engineering promises many new discoveries and may help solve many medical and biological problems; initial applications are already being made in the medical and industrial fields.

There is more awareness of the safety issues involved and many largely practical proposals to increase safety are being made.

Possibilities of Genetic Engineering

The scientific, social and economic importance of the new technology lies in the possibilities it offers for the following:

1. Obtaining specific sections of DNA in practically unlimited quantities.

   This is an important prerequisite for investigations into the microstructure of DNA. Modern biochemical methods make it possible to determine the sequence of nucleotides in DNA and thus read their genetic information. But this is only possible when specific pieces are available in large quantities. Thus, for example, in 1979 the microstructure of the DNA of the hepatitis B virus was worked out with the help of genetic engineering. As there is no way of propagating this virus in a culture, genetic engineering methods were the only way in which sufficient quantities of the virus's DNA could be obtained. Such work is an important step in developing a vaccine against this dangerous illness.

2. Understanding cell differentiation and the regulation of genetic expression, particularly in higher life forms.

   The fact that all the cells of a multi-celled organism, such as man, contain the same genetic information poses a largely unanswered question about how such information is utilized in a regular and orderly manner.

   This plays a part in embryo development, when it is established which cell will become a skin cell and from which cell a blood cell be produced (cell differentiation).

   In developed organisms, steps must be taken to ensure that only the genetic information related to the cell's function is used (regulation of genetic expression). Disturbances in cell differentiation and genetic regulation can lead to serious illnesses, such as cancer.

   Genetic engineering makes it possible to investigate the structure of specific nucleic acids in an individual organism and compare them with similar DNA segments in related organisms. At the end of such investigations one has an exact chart of all genetic information, which then makes it possible to identify the structures responsible for differentiation and regulation.

3. Deliberate transfer of specific hereditary information, and making it function in foreign organisms.

   This is the possibility which from the beginning has caused both the hopes and the fears. It is here that the information content of specific nucleic acids can be directly examined and it is here too that the economically interesting possibilities of applying genetic engineering lie. It is foreseeable that in this way therapeutically important products can be produced cheaply in easily propagated bacteria, e.g. pituitary hormones, antigens for vaccines or interferon.

4. A completely different application is the transfer of genes for specific functions into organisms which do not possess such a function naturally,

but which may be of great importance for such organisms. Thus, the introduction into plants of genes which make it possible to utilize nitrogen from the air would make such plants largely independent of fertilizers. Through the deliberate recombination of genes for specific characteristics one could produce, circumstances permitting, micro-organisms which, for example, attacked plastic or *"digested"* oil, which could be of great importance to keeping our environment clean.

Risks of Genetic Engineering

Genetic engineering makes it possible to combine genetic information from different sources into new viable units. In this way the genetic information of an organism can be expanded either at random or for a specific purpose. Host organisms can thus acquire new capabilities or characteristics. If these are characteristics that turn harmless organisms into pathogens or cause undesirable changes in our environment through whatever mechanism, then man and his environment can be endangered if organisms escape to the environment.

These factors led in 1973/74 to voluntary restrictions in the application of this technology by scientists and to the issue of national rules for recombinant DNA work. It must be pointed out here that these risks or dangers are only conjectural. All genetic engineering experiments carried out so far, and specific tests to assess the hazards, have failed to provide any evidence that these conjectural risks do in fact exist.

A formal analysis of the hypothetical risk indicates that genetically manipulated organisms will present a hazard only if the following conditions are met:

1. The host organism receives new genetic material; in all genetic engineering experiments, new genetic information is introduced into only a fraction of the host organism used.
2. The genetically manipulated organism escapes despite the experimenter's safety precautions. Long experience in working with highly pathogenic micro-organisms has shown that pathogens can be multiplied and examined without any danger to scientists or the environment.
3. A genetically manipulated organism that escapes must be able to:
   a) survive
   b) multiply, and
   c) interact with the living development

   indefinitely outside the laboratory or place of production.

Whereas animal cells, which are also suitable as host organisms, can continue continue to live and multiply only under very complex and stringent conditions never found outside a laboratory, lower organisms, such as

bacteria, yeasts and algae, can survive and reproduce under conditions that are not tightly controlled. This applies in particular to organisms that have recently been taken from their natural habitat and have not yet adjusted to artificial laboratory conditions.

But even the lower organisms have certain requirements, such as suitable temperatures, humidity, nutrients, etc., that must be met if they are to multiply.

In the case of some organisms, such as *Escherichia coli,* a normal inhabitant of the gut, the experimenter himself can form a suitable habitat and is thus particularly at risk.

If bacterial or animal viruses are used as recombinant DNA vectors, they must find a suitable host cell if they are to survive.

The extent to which organisms that have escaped will be capable of interacting with their environment depends on many special factors in the ecosystem. The probability of a genetically manipulated organism finding a suitable environment is in almost all cases extremely small. This particularly applies to weakened host organisms. With an appropriate choice of host organisms this probability can become close to zero.

4. If an organism established in the environment escapes after being genetically manipulated, it can become a hazard if the new DNA introduced imparts new harmful properties to it.

   Harmful properties include: Synthesis of harmful substances (e.g. tetanus toxin) by bacteria, acquisition of a particularly high growth potential in the case of weeds, and the ability to pass on foreign, potentially dangerous nucleic acids to the actual target cell (e.g. tumor viruses).

   Only if all the above conditions are fulfilled can the conjectural dangers become a reality. The actual probability of this happening is equal to the product of the probabilities of conditions 1 to 4.

   If we confine ourselves to the risk of genetic manipulation turning a harmless micro-organism into a microbe producing a dangerous infection, then the following requirements can be added to the above conditions:

   a) Survival and reproduction must take place in such a way that transmission is possible from animal to animal or from one human being to another;
   b) The microbe must have the ability to penetrate the skin or the mucous membranes and must be resistant to the natural defence mechanisms, such as interferon;
   c) The microbe must be able to multiply and spread in the infected host;
   d) The microbe must be able to produce a toxin or harm the host in another way.

All these preconditions must be met simultaneously for the danger to materialize.

This formal analysis of the risk involved not only explains the probability of something dangerous occurring but also gives some pointers as to what safety measures are suitable for reducing or removing altogether the risks to man and the environment posed by genetic engineering experiments or the use of genetically adapted organisms.

Assessment of the Risk

The conceivable or conjectural risks of genetic engineering range from a danger to the experimenter or other parties to a life-threatening change in the environment.

On the basis of an analysis of special experiments to assess the risks and a re-evaluation of longstanding experience and knowledge, the actual risks are today considered to be very slight.

While it was initially assumed that practically all DNA introduced at random by genetic engineering would lead to a change in the characteristics of the host organism, the numerous genetic engineering experiments carried out so far have shown that this in fact happens in very few cases only.

Part of the genetic information of all organisms is a complicated control system, into which the foreign DNA must be fitted very carefully if it is to be effective. This means that the experimenter can in many cases predict when the host organism can be expected to acquire new properties.

Particular concern was felt previously about the transfer of DNA from animal cells to lower organisms. There were fears about the uncontrolled introduction of genetic codes for malignant degeneration or highly active hormones, for example, into lower organisms, which could then lead to the formation of tumours or hormonal disorders in humans. It was subsequently discovered that the genetic information of higher organisms is not present in one continuous piece but is divided into many sections with gaps in between. Before such fragmented information is utilized it must be joined together in a complicated process. This structure of the genome makes the accidental transfer of potentially dangerous genetic information practically impossible, especially as bacteria are not in a position to process the genetic information contained in the sections.

Obviously, there was also a fear that the introduction of genetic information from pathogens or poison-producing plants and animals could give host organisms new, pathogenic characteristics. Accordingly, all such experiments have, from the outset, only been conducted using special safety precautions.

Investigations into the factors which determine the pathogenic qualities of viruses and, in particular, bacteria show that several features must always be

present at the same time if such organisms are to become a danger. As it is improbable that all the necessary factors are acquired at the same time by the host organism in a single genetic engineering experiment, the risk of such an event occurring is considered to be relatively small. But if one is still advised to be careful here, it is because our knowledge of the process through which micro-organisms cause illness is still very incomplete.

A distinction must be made between the uncontrolled risk of transferring random genetic information (*"shotgun experiment"*) and the risks that can arise with the selective introduction of characteristic genetic information into host organisms. In many cases the risk here can be very accurately assessed or specific tests can be carried out to evaluate it. Suitable safe precautions can then be taken to counter the special hazards.

There has been no shortage of attempts to classify the possible risks which may be involved in working with organisms containing recombinant DNA.

The aim of such attempts is to correlate certain risks with certain safety measures. Unfortunately, none of the suggested classification systems has completely solved the problems involved because many of the parameters necessary can only be specified approximately. Very soon it will be possible to apply the verifiable and tested rules of medical microbiology.

In the Member States, either the classification of the USA's NIH or the UK was taken over or separate national guidelines were drawn up (as in West Germany, for instance). Common to all the various guidelines is the fact that work with pathogenic micro-organisms, the genes of poisons or highly active proteins (e.g. hormones) is considered to be particularly hazardous.

In 1979, a WHO working party proposed a classification of pathogens which could also be applied in genetic engineering. This is possible if one assumes that organisms with recombinant DNA pose dangers similar to — but not greater than — those posed by known pathogens. In the WHO classification, known pathogens are divided into four risk groups.

Risk Group I: Low risk for individuals and the general public

Organisms which as a rule do not cause illnesses in human beings or animals. To this group belong the much-used host organisms *E. coli* (normally found in the intestine) or *B. subtilis* (a common germ found in the soil).

Risk Group II: Moderate risk for individuals, limited risk for the general public.

An organism which causes illnesses in human beings and animals but which, as a rule, does not represent a serious danger for those working in laboratories, the general public, the animal world or the ecosystem. Contact with such organisms in the laboratory leads only rarely to serious infections; effective preventive measures and medicines are available and the risk of propagation is limited.

Risk Group III: High risk for individuals, low risk for the general public

An organism which usually causes serious diseases but which, as a rule, is not transferred by an infected person to others.

Risk Group IV: High risk for individuals and the general public

An organism which, as a rule, causes serious diseases in human beings and animals and which can be easily transferred directly or indirectly.

This classification system considers the following criteria as important in determining to which risk group a pathogen should belong:

— the frequency that a pathogen causes an illness;
— how dangerous the disease is, and
— the probability of the disease being transferred.

Thus the rubella virus, for example, which as a rule does not cause a serious disease, which represents a danger only for pregnant women who have no immunity and for which an effective vaccine is available would belong to Risk Group II.

The rabies virus, which always causes deadly infections but which is not transferred from one human being to another, would go in Risk Group III.

Germs which cause hemorrhagic fevers (e.g. Lassa or Ebola virus) or the smallpox virus would belong to Risk Group IV.

Genetic engineering work will generally fit very neatly into this scheme. Experiments using weakened host organisms (safe strains) which are highly unlikely to be capable of reproducing themselves outside a laboratory will normally be put in Group I, and rarely in Group II.

Genetic engineering work which has the purpose of producing highly active proteins (e.g. hormones) is classified according to the suspected risk of an infection being produced by the resulting host organisms, as established on the basis of medical experience.

In genetic engineering work with pathogens, e.g. with the aim of making a vaccine, experiments should first be assigned to the same Risk Group as the pathogen involved. Reclassification is always possible in the light of experience.

Safety Measures

Although the possible hazards of genetic engineering are today considered to be very slight, they cannot, however, be completely ruled out. This means that suitable safety precautions must be taken to deal with the conjectural risks.

Genetic engineering safety precautions must above all be aimed at preventing the escape of a host organism and/or making it impossible for the host organism to become established in the environment. This is achieved by:

1. Observing *"good microbiological practice"*;
2. Applying special physical safety precautions;
3. Using weakened host organisms that can only multiply under controlled conditions (biological safety precautions).

Ad 1

Strict application of proven techniques for working with micro-organisms, particularly pathogens, is the most important safety precaution of all. Its effectiveness is underlined by the fact that work on pathogens has been going on for over 100 years without any major chains of infection having started in the laboratories in question. Any occasional infections of the persons working directly with the microbes has always been due to non-observance of *"good microbiological practice"*.

This includes above all a strict ban on pipetting by mouth and on eating, drinking and smoking in the laboratory; the hands should also be washed thoroughly before leaving the laboratory.

Sound training in *"good microbiological practice"* must be given to all staff before they start genetic engineering work, and this training must be repeated at regular intervals. As part of this training, staff must be instructed how to act in emergencies.

All persons engaged in genetic engineering must be familiar with decontamination and disinfection techniques.

Ad 2

Operations whereby aerosols containing micro-organisms occur can be carried out without any particular risk in special safety cabinets (Class I, II and III). The negative air pressure in these safety cabinets ensures that microbes cannot get out. Filters impermeable to bacteria prevent the organisms from escaping with the flow of air. Any desired containment of the micro-organisms can be achieved with appropriate set-ups. Use of these facilities does, however, mean considerable constraints in the performance of the experiments.

If these safety cabinets are used in specially designed safety laboratories under negative air pressure and with outlet air filters, it is practically impossible for genetically manipulated organisms to escape, provided *"good microbiological practice"* is constantly observed.

Ad 3

If genetically manipulated micro-organisms or vectors are to form a hazard they must be able to establish themselves in their normal environment. Shortly after the introduction of the new technology, the scientific world

therefore proposed that in genetic engineering work, use should be made only of hosts and vectors with defects, so that they are able to live and multiply only under artificial conditions.

Animal cells in cultures are therefore ideal hosts. Similar suitable hosts have been produced by introducing certain mutations in micro-organisms that have been well investigated. Mention can be made here of strains of *Escherichia coli, Bacillus subtilis, Streptomyces cœlicolor* and *Sacharomyces cerevisiae.*

All these "*safe*" strains are defective in one or more properties essential for survival under natural conditions.

Constant checks must be made to ensure that it is in fact these "*safe*" strains that are being worked with. This is to prevent non-weakened strains from being contaminated and overgrown with wild strains.

Health Protection

The persons coming into closest contact with genetically manipulated organisms are those engaged in genetic engineering work. It is therefore reasonable to assume that these are the persons most likely to be at risk. Persons who are especially at risk, such as pregnant women, persons with diseases of the immune system and persons undergoing cytostatic treatment, should be excluded from genetic engineering work that could put them in danger. For this reason, a careful examination when staff are recruited or when genetic engineering work is begun is of great importance. Serum samples should be taken and kept for comparison in later tests. Permanent, specifically directed health supervision is an important measure here for averting risks and detecting special hazards.

Selective investigation of certain medical parameters, such as antibody count or resistance to antibiotics of the natural flora can indicate whether a dangerous event has taken place. In this way health supervision can help to check the effectiveness of the safety precautions.

State Monitoring of Genetic Engineering

The introduction of this technology sparked off a debate on whether it is the State's job and/or duty to regulate and monitor genetic engineering.

Almost all countries promoting research have issued rules for work with recombinant DNA. Some countries have so extended existing epidemics legislation that genetic engineering is also covered.

The most important elements in the rules are registration of genetic engineering work, restriction to selected host organisms and vectors and the designation of special safety precautions for certain conjectural risks.

As more and more experience has been gained with genetic engineering, the restrictions imposed by the rules have been eased. Some countries think that registration is enough, but others continue to engage in very extensive monitoring of these experiments. At all events it will not be possible in the foreseeable future to dispense with State licensing in the area of biological safety precautions, i.e. the use of selected hosts and vectors. The strict observance of biological safety precautions has made a decisive contribution towards ensuring that the initial fears about the dangers of the new technology have so far not become reality. Because of the great, indeed decisive, importance of biological safety precautions, the choice of them cannot be left to individual researchers.

Final Comments and Open Questions

The debate on the uses and risks of genetic engineering has many peculiarities and despite the great intensity with which it has been conducted, many questions have been left open.

It is worth noting that it was the scientists concerned themselves who drew attention to the possible dangers of the new technology in open letters (1973, 1974). They called upon the relevant national authorities to lay down guiding principles for work with organisms containing recombinant DNA. Until then, the nature and extent of experiments were to be regulated through voluntary restraint.

The national authorities have tackled the problems involved with noticeable rapidity and thoroughness, and it is clear how attitudes towards science have changed. Instead of an almost unbridled enthusiasm for all things scientific, there is now a widespread attitude of almost instinctive scepticism towards any new scientific development. Any critical assessment of the state of genetic engineering must take into account this changed attitude towards science on the part of the public. Scientists themselves consider the new technology to be highly important. Many hitherto insoluble problems can be tackled. Consequently, we are now finding more and more applications for genetic engineering techniques.

The reactions of the public have varied enormously. Some highly motivated groups have thrown themselves into the debate intensively and aggressively, while others have simply become confirmed in their mistrust of science. The new discoveries and methods have not always been adequately represented in the press. Exaggerated reports of the commercial usefulness of genetic engineering have particularly aroused public mistrust. Many fear that safety measures necessary to protect the public are being sacrified for the benefit of supposed economic interests.

While the problems of genetic engineering were first intensively discussed only in the small world of molecular genetics, in the course of the debates

medical microbiologists, population geneticists, ecologists, infection experts and other scientists have been drawn into the discussion. This has proved extremely fruitful for all the scientists involved. A new, more realistic assessment of the risks would not have been possible without such wide-ranging cooperation.

But despite these efforts many questions remain open, as the discussion about the Council Directive has shown. Many questions must remain unanswered because none of the experiments necessary to finding an answer have yet been performed. Other, perhaps important questions have been asked because the full range of possibilities for applying the new technology is not yet known. Where possible, a decisive attempt should be made to discuss the problems involved without prejudice in a dialogue between scientists and the general public and find conclusive solutions.

Among the questions which are still open or which have not been explained adequately are the following:

— Are the risks of genetic engineering being assessed realistically today by scientists?
— Are the risks of genetic engineering balanced by its uses?
— Should further investigations into the risks of genetic engineering experiments be carried out?
— Are we monitoring the field of application of the new technology so well that we can take account of all possible risks?
— Is it possible to draw up a reliable classification of the risks and use it to classify safety measures?
— Are supervisory measures indicated to ensure that only weakened host organisms and the corresponding vectors are used in genetic engineering work?
— Should all genetic engineering experiments be notified and registered or not?
— Must certain experiments be made dependent on prior authorization by the state authorities?
— Do genetic engineers receive adequate basic and further training on safety techniques?
— Is it possible and recommendable to codify "*good microbiological practice*"?
— Are the physical safety measures currently being practised adequate, inadequate or exaggerated?
— Must the use of only specially weakened organisms (safe strains) be maintained?
— Does the commercial use of this technology involve particular risks?
— Is the commercial use of this technology helped or hindered by having different rules in the Member States?

— When should the State step in to protect the general public?
— What measures can the State take to make full use of genetic engineering techniques?
— What steps can be taken to ensure that this new technology does not encourage new power structures and thus limit the general public's freedom and power of decision?
— Is it ethically permissible to use genetic engineering to change a person's hereditary characteristics, e.g. by remedying a genetic deffect?
— What steps can be taken to ensure that the general public are informed critically, accurately and adequately about genetic engineering?

GLOSSARY

Aerosol	:	Mist-like distribution of very fine droplets of liquid or solid particles in a gas, mostly in air.
Amino acids	:	The building blocks of proteins. There are twenty amino acids. They are joined one at a time, like beads on a string, as the final step in the translation of DNA's genetic message.
Antibiotic resistance	:	Resistance of a bacterium to the deadly or restrictive effect of an antibiotic. May occur through mutation in the genome of bacteria, but usually transferred by plasmids.
Antigens	:	Substances which can be identified as foreign by human beings or animals and are combatted by antibodies.
Antibodies	:	Substances produced by animals or human beings to defend the body against antigens.
Antibody count	:	Surveillance of the type and number of recorded antibodies.
B. subitilis (Bacillus subtilis)	:	Harmless bacterium found in the soil.
Bacteria	:	Small, one-celled organisms with a single chromosome which is not enclosed in a nuclear membrane.
Bacteriophages	:	Viruses that reproduce within bacterial cells and infect new cells following the breaking open of the old ones.
Cell differentiation	:	Process, notably in embryo development, whereby a basic cell is changed into cells with specific functions.
Chromosomes	:	Thread or rod-shaped elements in the nucleus of a cell which harbour hereditary factors (nucleic acid).
Clone	:	A group of genetically identical cells or organisms asexually descended from a common ancestor. All cells in the clone have the same genetic material and are exact copies of the original.

Disinfection	:	Destruction of micro-organisms through heat treatment or chemical methods.
Decontamination	:	Removal of polluting microorganisms from working surfaces, premises, containers, etc.
DNA (Deoxyribonucleic acid)	:	The genetic material found in all living organisms. Every inherited characteristic, every genetically produced function, has its origin somewhere in the code of each individual's complement of DNA.
Embryo development	:	Typical development of an animal or human being from a fertilized egg cell.
Enzymes	:	Complex protein structures which trigger chemical changes in living cells.
E. coli (Escherichia coli)	:	A harmless bacterium which occurs naturally in the intestine of human beings and animals.
Eukaryotes	:	Organisms having cells containing a defined nucleus, multiple chromosomes, and a defined mitotic apparatus. Eukaryotes can be either unicellular (yeasts, protozoa) or multicellular (animal and plants).
Gene	:	The smallest section of a chromosome which contains the hereditary information for a protein.
Genome	:	The sum of all the genes in an organism; corresponds to the chromosome in bacteria or to the chromosomes in higher organisms.
Genetic code	:	Alphabet of hereditary factors. The sequence of three nucleotides in each case determines one of the 20 amino acids.
Genetic expression	:	Process in which genetic information is translated into a product.
Germ cells	:	Cells produced and set aside early in development to produce sex cells or gametes. In higher animals only changes produced in germ cells or their descendants can be transmitted to the next generation.
Hemorrhagic fevers	:	Severe, often deadly viral infections which are accompanied by heavy bleeding.

Hormones	:	Highly active proteins which are formed in one place in a multi-celled organism and have their effect in another.
Host cells	:	A cell in which a virus grows and reproduces. In recombinant DNA experiments, the host cell is usually a bacterium, like *E. coli*, into which a virus containing hybrid DNA is inserted.
Hybrid	:	Plant or animal resulting from a cross between parents that are genetically unlike; often restricted to the offspring of two different species or of well-marked varieties within a species.
Interferon	:	Protein liberated by cells during an infection which protects other cells unspecifically, especially from a virus infection.
Malignant degeneration	:	Transformation of a normally growing cell into a cancerous one.
Micro-organism	:	Microscopically small organism; unicellular plant animal or bacterium.
Mutation	:	Inheritable change in the genome.
Nucleic acid	:	Basic chemical substance for hereditary information, long thread-shaped molecule from intertwined nucleotides.
Nucleotides	:	Building blocks of a nucleic acid, consisting of sugar, phosphate and one of the following four organic bases: adenine, cytisine, guanine and thymine.
Pathogen	:	Parasitic organism which causes disease.
Phenotype	:	The characteristics of a given organism resulting from the expression of its genotype in development under particular environmental conditions.
Plasmids	:	Ring-shaped nucleic acids in micro-organisms with hereditary information which multiply independently of the chromosome and can be exchanged between bacteria.

Procaryote cell	:	The less complex cell type found in bacteria and blue-green algae. To be distinguished from eucaryote cells, containing a membrane-founded nucleus and found in all other organisms.
Protein	:	A large molecule composed of amino acids. Proteins, in structural and functional forms, are both building blocks and the catalysts for change in living organisms.
Recombinant DNA	:	DNA molecules of different origin that have been joined together by biochemical techniques to make a single molecule, usually circular and usually capable of some specific biological function, especially self-replication in an appropriate cell.
Restriction enzymes	:	Enzymes which divide nucleic acids up at specific points determined by the sequence of their nucleotides.
RNA (Ribonucleic acid)	:	In its three forms - messenger RNA, transfer RNA, and ribosomal RNA — it assists in translating the genetic message of DNA into the finished protein.
Somatic cells	:	The cells of which the body of an organism is constructed, as opposed to the reproductive or germ cells.
"Shotgun experiment"	:	Use of random nucleic acid segments of a genome in a genetic engineering experiment.
Toxins	:	Highly effective poisons formed by certain micro-organisms, plants or animals.
Tumor viruses	:	Viruses which can change a normal cell into a cancerous one.
Vector	:	A vehicle for transmission of a replicative agent from an infected to a non-infected host. In recombinant DNA, specifically a plasmid or virus that can carry a foreign DNA into a host cell.
Virus	:	A disease-producing particle consisting of nucleic acid and protein which can only multiply in living cells.

European Communities — Economic and Social Committee

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On 14 and 15 May 1981, the Economic and Social Committee, forum of the interest groups in the European Community, held a colloquy on *"The Safety Aspects of Recombinant DNA Work"*. It was the first international meeting on genetic engineering at European level to include representatives from the fields of government, science, industry, trade unions, consumers, environmentalists, religious, youth and women's groups. Its purpose was to facilitate information-exchange in accessible language.

The proceedings record the papers and discussion under six separate topics: development potential, risks and risk assessment, safety, health protection, ethics and public information. The appendix provides a background Study drawn up within the Economic and Social Committee at the end of 1980.

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