ORGANISATIONAL HAZARDS IN BIOTECHNOLOGY — TOWARDS A NEW RISK ASSESSMENT PROGRAM

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Great progress in the field of recombinant DNA technology has masked concern about the safety of the procedures involved. It seems that those carrying out oncogene research using these techniques may be exposed to considerable danger of contracting cancer. A thorough program to assess the risks involved is required to replace the complacency of ignorance which now exist, and it is required before rather than after damage is done.

Keywords: oncogenes, risk assessment, recombinant DNA technology, genetic engineering

INTRODUCTION

When scientists discuss the safety of recombinant DNA technology, they invariably contrast the naivety and uncertainty that coloured the picture *then,* with the sophistication and assuredness they have *now,* where 'then' refers to the dawn of genetic engineering in the mid-1970s, around the time of the Asilomar Conference.[1] The familiar argument runs as follows: then we *suspected* that recombinant organisms might constitute a biohazard, but by contrast now we *know* that recombinant DNA manipulations are safe. On this view the only challenge that remains in the area of recombinant DNA safety is to convince the non-scientific public that all is safe and well in hand.[2]

But perhaps not all is safe and well. As recently as June 1986 it was reported in the scientific press that at the Pasteur Institute in Paris five molecular biologists involved in cancer research who worked in one wing of a building had contracted cancer at about the same time.[3] Two have died and the other three are seriously ill. In order to come to grips with the unexpectedness of this cluster of cancer cases amongst molecular biologists, the International Agency for Research on Cancer has called for an international epidemiological study to evaluate the risks facing molecular biologists working in the area of cancer research.[4] While this will no doubt turn out to be an interesting study, more positive action can also be taken at this stage. This would

involve establishing a new risk assessment program with a focus on the occupational hazards facing molecular biologists engaged in cancer research, particularly those who manipulate cancer genes (oncogenes).

Oncogenes are a rather new addition to molecular biology, in that their study and characterisation has been possible only from 1980 onwards. By that time the technology of recombinant DNA research had become sufficiently well developed to tackle this complex field, and the guidelines pertaining to recombinant DNA work had been relaxed to the extent that cancer genes could be produced and studied in the laboratory with minimal requirements for containment.[5]

In the brief period since 1980, an impressive amount has been learned by molecular biologists about oncogenes and their role in cancer causation. Furthermore, there are very close links between this research and commercial biotechnology. Indeed, much basic research involving oncogenes is conducted in the private sector, and in the United States alone a dozen new biotechnology companies are active in this area.[6] But the intense activity in oncogene research and in its commercialisation also has a negative side. If there are occupational hazards involved in working with oncogenes, then the number of people at risk is substantial. On this basis, it becomes essential that a systematic program of risk assessment be conducted which ascertains whether there are hazards and where they lie, and which is then followed by the implementation of safety precautions for all the workers involved in the manipulation of oncogene material. Only on that basis will it be reasonable to assert that oncogene research is not only exciting and profitable, but also free from occupational hazards.

In this paper I begin by discussing some of the reasons why molecular biologists feel secure in their assumption that recombinant DNA experiments are safe. I then summarise past recombinant DNA risk assessment discussions and experiments, pointing out that none of these dealt directly with the question of oncogene hazards. In Section 3 a very brief outline is provided of the nature of oncogenes, which hopefully will ensure that non-specialists can follow the arguments in the next two sections, where I present my concerns about occupational safety in oncogene research. The final section centres on the need for a new oncogene risk assessment program and sets out some guiding principles for its implementation.

FEARS ABOUT RECOMBINANT DNA AT THE TIME OF ASILOMAR

It is important to establish from the start that I agree with thousands of molecular biologists around the world that the suspicions and fears of the early 1970s about recombinant DNA safety have by now largely been laid to rest. However, new and unforeseen problems have arisen,

and our confidence that we have dealt adequately with the old problems must not prevent us from attributing sufficient weight to the newly emerging difficulties.

Back in the days of the Asilomar Conference, recombinant DNA biohazards were conceived in terms of an exotic diseases scenario. It was feared that genetically engineered bacteria would be unique, and could therefore bring about unforeseen diseases in epidemic proportions. The fears that prevailed at the time are well captured in a quotation from journalist Michael Rogers from his description of the Asilomar Conference:

> The long imprisoned *E.coli,* laden with a brand-new bit of biological activity, suddenly finds itself liberated; floating in a minute droplet on a technician's finger, then onto a tuna-fish sandwich, and thence into a luckless human gut. Or, in a culture not quite completely killed, down some stainless steel laboratory sink, and thus into a sewer system teeming with billions of close relatives.
> And now what? Precisely what could our artificially mutated *E.coli* do with its sudden freedom?
> An epidemic cancer that spreads through the sewer system? A once conquered disease like bubonic plague, now abruptly, again incurable? Or a brand new disease, sudden and mysterious, that has never before appeared in human being?[7]

Now we know the answer to Rogers's question about what the artificially mutated *E.coli* could do with its sudden freedom. The answer is not much — no cancer epidemic, no plague and no brand new disease. Moreover, we can be pretty sure that our answer is correct because our evidence derives from the experience of molecular biology laboratories around the world. In the last decade, *E.coli* with brand new bits of biological ability have been handled in hundreds of laboratories, by thousands of scientists and technicians. Over and over again, such *E.coli* must have floated onto tuna-fish sandwiches, into human guts, down laboratory sinks, and into the sewer system. And on the face of it — at least until the recent problems at the Pasteur Institute — nothing untoward seems to have happened. On the basis of this day to day experience. I feel that we can be reasonably confident that *normally engineered* bacteria which contain bits of recombinant DNA do not present a biohazard.

THE PAST RECOMBINANT DNA RISK ASSESSMENT PROGRAM

In addition to the ongoing work in molecular biology laboratories around the world, there has also been a certain amount of official recombinant DNA risk assessment carried out, primarily under the auspices of the United States National Institute of Health (NIH). The

most important elements of this program can be summarised as follows:

OCCASION	DATE	SCIENTIST IN CHARGE	METHODOLOGY	FINDINGS
Falmouth Conference	June 1977	S.L. Gorbach	Discussion among experts	Low chances of survival of laboratory strains of *E.coli*[8]
Ascott workshop	Jan. 1978	M.A. Martin	Discussion among experts	Bacteria containing cloned virus DNA do not produce active virus particles.[9]
'Worst case' risk assessment	1978	M.A. Martin	Experiments using the virus Polyoma	Bacteria containing cloned polyoma DNA are not infectious and not tumorigenic.[10]
Retrovirus risk assessment	1980	M.A. Martin	Experiments which have not been published	Bacteria containing cloned retrovirus DNA are not tumorigenic.[11]
Pasadena workshop	April 1980	L. Sherwood	Discussion among experts	If insulin-producing bacteria were to colonise the gut, 25 micrograms of protein would be released in the human gut per day.[12]
Gut colonisation risk assessment	1980	S.B. Levy	Experiments	Commonly used plasmids are not transmitted out of *E.coli* into other gut bacteria.[13]

Many of the risk assessment studies summarised here have been looked at critically by researchers who do not subscribe to the status quo view that recombinant DNA work has been proved to be safe. Susan Wright[14], Sheldon Krimsky[15], Barbara Rosenberg[16], Hiro Sibatani[17] and I[18] have pointed out that in the various risk assessments there have been a multitude of unlikely assumptions, unwarranted conclusions and statistical sleights of hand. Moreover, this critical work has shown that the scientists involved in the risk assessments have been most effective in disseminating into the political arena a

message of recombinant DNA safety which goes well beyond the conclusions that can be derived legitimately from the risk assessments themselves.

In this paper I do not wish to dwell on the details and the shortcomings of the risk assessment experiments and the discussions summarised above. Instead, I will consider in detail a new set of potential hazards outside the scope of this past program. The potential hazards we shall be dealing with here derive from a research area within molecular biology which was explored only *after* the past program of risk assessment was completed. This new area of work, which began around 1980, is the study of cancer genes (oncogenes). It is a research area that has been exceedingly useful for understanding the mechanisms by which cancer is caused, and it is expected that further advances will follow rapidly. But interestingly, the research findings themselves indicate that if oncogene material — isolated and purified by means of recombinant DNA technology — gains a foothold in persons who work with this material, then the workers themselves could become cancer victims.

It is important to recognise that the past risk assessment experiments and discussions had been completed before oncogene research began, and could, therefore, not have been designed to determine whether oncogene material presents an occupational hazard. For this reason, it is important to set up a new risk assessment program which is devoted to determining experimentally where the risks from oncogenes lie, and to consider how to arrange working conditions so that the manipulation of oncogenes is safe.

BRIEF INTRODUCTION TO THE STUDY OF ONCOGENES

Oncogenes are now regarded as the key triggers in the development of cancer.[19] They are genes in the normal sense, in that they are made of DNA, and code for protein products — the oncogene proteins — which act in such a way as to turn cells cancerous. Currently, several theories on the action of oncogene proteins are being explored, but these need not concern us here. The oncogenes themselves, as well as the oncogene proteins, seem to occur in a normal state in normal cells, where they fulfil important cellular roles, most likely dealing with the regulation of cellular growth and development. But the normal oncogenes can become altered or activated, and then much larger quantities of oncogene proteins are produced, as well as modified forms of these proteins, and it is these altered conditions which bring about the cancerous state.[20] Again, the details are quite complicated, and are being studied actively in many laboratories around the world.

Since about 1980 it has been possible to extract activated oncogenes from human cancer tissue. For example, the oncogene called *ras* has

been purified from human bladder cancer tissue, and it is accepted that *ras* is in some way responsible for the development of bladder carcinoma.[21] About 20 oncogenes have now been identified and purified, all of them linked to one or another human or animal cancer. The purification of oncogenes, as well as their further characterisation, involves their cloning and re-cloning, and, in general, oncogene research is impossible to imagine in the absence of the recombinant DNA technique. It should also be said that most of these cancer-derived oncogenes can be incorporated into a special class of viruses, the tumour viruses or retroviruses. In practice the manipulation of oncogenes and retrovirus work go hand in hand.

In the last few years an enormous body of research has been conducted in the field of oncogenes, and these brief comments will obviously not go very far in fostering familiarity wth this mass of work. They should, though, suffice to provide a background to the points I wish to raise about the safety of manipulating oncogene material.

CONCERNS ABOUT OCCUPATIONAL HAZARDS IN THE MANIPULATION OF ONCOGENE MATERIAL

One of the first questions that arises when we consider the safety of oncogene research is whether oncogene DNA, isolated by means of the recombinant DNA technique, is safe to handle. Let me briefly point to some observations which indicate that oncogene DNA material could endanger those who work with it.

A basic test in oncogene research involves the addition of oncogene DNA, extracted from cancer tissue, to a common laboratory cell line which is called NIH3T3. Some activated oncogenes (for example, *ras*) will make the NIH3T3 cells cancerous. This process is called *transformation*. We may then ask: if certain oncogene DNA material transforms, that is to say turns cancerous some cell types growing in tissue culture, is such a change also likely to occur in the intact organism (for example, in the laboratory worker)?

It is reassuring to know that the analogy between the NIH3T3 cells and the laboratory worker does not hold in a straightforward way. The reason is that the NIH3T3 cells are already in a so-called 'precancerous' state, meaning that by experimental manipulation they can be turned into cancer cells more easily than normal cells. In other words, the NIH3T3 cells are already halfway along the path to cancerous transformation.

Recently, however, oncogene research work has been extended so that now not only precancerous cells, but also normal cells can be transformed to the fully cancerous state by means of the addition of oncogene DNA. What is involved is two oncogenes being added

together, in particular the oncogenes designated *ras* and *myc*.[22] In these experiments, first performed by Professor Weinberg and his colleagues at MIT in 1983, normal cells growing in culture turn cancerous due to the addition of oncogene material. The analogy between the cell culture and the living organism (say the laboratory worker) is obviously becoming much closer. What emerges from this analogy is that oncogene DNA material, harvested from cancer tissue with the aid of recombinant DNA technology, could turn out to be a substance that is hazardous to handle. The following Table summarises this work:

TABLE 1

Oncogene	**Cell System**	**Outcome**
ras	precancerous cells	transformation
myc	precancerous cells	no transformation
ras	normal cells	no transformation
myc	normal cells	no transformation
ras + *myc*	normal cells	transformation

The work of Weinberg and his colleagues shows that if the DNA of two particular oncogenes is combined (namely the DNA of the oncogene *ras* and the oncogene *myc*), and the DNA mixture is added to normal cells growing in culture, then these cells are transformed to cancerous cells. The following question then arises: would such an oncogene DNA mixture evoke the same response if the normal cells were located not in tissue culture but in living animals? In other words, would the injection of such an oncogene mixture into a living animal bring about transformation *in situ*; that is, would it induce cancer? Strange as it may seem, no experiments have yet been reported anywhere to answer this apparently straightforward question, a question which is of obvious relevance to an assessment of whether oncogenes are hazardous to handle.

However, an approximate answer can be provided, based on experimental work conducted in the field of oncogene research itself. In 1983, Fung and his colleagues reported from the University of California at San Francisco that when activated oncogene DNA of the *src* type was injected into chickens, small tumour nodules developed at the injection sites.[23] Interestingly, the oncogene used in this experiment, namely *src*, is similar to the *ras* oncogene in that in a cell culture system both of these oncogenes will transform only the

specialised, precancerous NIH3T3 cells, and not normal cells. Nevertheless, when *src* oncogene DNA was injected into the animals, tumour nodules were formed at the injection site.

It is obvious that experiments along the lines of Fung's work should be performed in the interests of safety. For example, would the oncogene injection experiment be even more convincing if a combination of oncogenes were used, let us say *ras* and *myc*? Would the tumours be larger? Would they be of the spreading type and kill the animal? The relevant information can be tabulated as follows:

TABLE 2

Oncogene	System Tested	Outcome
src	precancerous cells	transformation
src	normal cells	no transformation
src	intact animals	tumour nodules
ras + *myc*	precancerous cells	transformation
ras + *myc*	normal cells	transformation
ras + *myc*	intact animals	?

This table highlights some of my concerns about the safety of recombinant DNA manipulations with oncogenes. It points out that on the basis of findings generated in the oncogene research field itself, we can make the reasonable prediction that the injection of certain oncogene combinations into living organisms could lead to the induction of cancer. If such a prediction were to be corroborated in the laboratory, this would have serious implications for the safety of those engaged in the manipulation of oncogenes. But as yet there has been no risk assessment conducted to establish experimentally whether the prediction holds. Thus, at the moment we are faced with a situation in which some experimental findings indicate that oncogene DNA material could be hazardous in an occupational sense, and yet this concern has not been laid to rest, and neither has the extent of the potential danger been determined experimentally.[24]

FURTHER CONCERNS ABOUT OCCUPATIONAL SAFETY: THE PRODUCTION OF ONCOGENE PROTEINS IN RECOMBINANT BACTERIA

I would now like to turn to another research front in oncogene investigation which is also relevant to concerns about occupational

safety in oncogene manipulation. Indeed, from an occupational point of view, this area is even more pertinent since this work has direct commercial implications. Here we are dealing with the deliberate production of genetically engineered bacteria which are highly efficient at synthesising so-called oncogene proteins. What happens is that novel bacteria are designed in such a way that they constitute mini-factories for the production of those proteins which are believed to be directly involved in the mechanisms by which cancer arises.

The oncogene proteins are the cellular products of the oncogenes and they are the biochemical agents that in some way bring about carcinogenesis. In the last year or so, research has progressed to the point where oncogene proteins can now be manufactured in recombinant bacteria and harvested from them. In other words, the proteins specified by the oncogenes we have encountered before, namely *ras, myc* and *src*, have all been 'expressed' in genetically engineered *E.coli* cells. Furthermore, the recombinant bacteria have been engineered so that they are extremely efficient at producing oncogene products.[25]

It was the aim of the NIH workshop held in Pasadena in 1980 to determine whether *E.coli* bacteria which are genetically engineered to manufacture certain biologically active proteins (for example, insulin) constitute a hazard.[26] First, the workshop participants were asked to assume that in the case of an accident, all the *E.coli* of the gut would become insulin-producing, but none of the other gut bacteria. It is known that *E.coli* bacteria make up only 1 per cent of all the bacteria in the gut, and so on this assumption about 2×10^9 cells would become involved in insulin production. Second, at the Pasadena workshop it was also assumed that the bacterial protein production would proceed at the rate of 1 million protein molecules in each bacterial cell in a generation of bacterial growth.

With this background in mind, it was then calculated at the risk assessment workshop that if insulin-producing bacteria were to colonise the gut in the proportions indicated above, then insulin would be produced at the daily rate of about 50 micrograms or 0.6 units. To put this in context, a normal human being produces about 25 units of insulin in the pancreas every day, so it is fair to say the 0.6 additional bacterially produced units of insulin would not make a great deal of difference. Now let us look at the case where the engineered bacteria synthesise not insulin, but rather oncogene proteins. A number of oncogene researchers have reported recently that they have achieved a high level production of oncogene proteins in bacteria, in many cases amounting to 10 per cent of the total bacterial protein being the synthesised oncogene protein.

For the sake of consistency, let us make the same assumptions in this theoretical risk assessment exercise as were made at the Pasadena

workshop. Thus, we shall again assume that following a hypothetical occupational accident the oncogene synthesising *E.coli* come to colonise the gut so that all the *E.coli* of the gut begin to produce oncogene proteins, but the other 99 per cent of gut bacteria do not. Also let us assume a synthetic activity of 1 million oncogene protein molecules per bacterial cell per generation, which is quite consistent with the 10 per cent protein ratio mentioned above.

On these assumptions, and taking the molecular weight of an oncogene protein as 21,000, we arrive at an approximate yield of 25 micrograms of oncogene protein produced in the gut every day. This is a similar figure to that arrived at by the participants at the Pasadena risk assessment workshop with respect to potential insulin production in the gut. But whereas 25 or so micrograms of insulin produced in the gut makes little difference, since humans produce much larger amounts of insulin every day, the situation is far more worrying with respect to oncogene proteins. Current oncogene research indicates that these proteins are the key triggers in the transformation of normal cells to cancer cells. Furthermore, unlike the case with insulin, there is certainly no abundance of oncogene proteins in the normal organism. Hence the production of oncogene proteins at the rate of 25 micrograms per day in the human gut could constitute an occupational hazard of great proportions.

THE NEED FOR A NEW ONCOGENE RISK ASSESSMENT PROGRAM

I have pointed to two areas of occupational concern in work with oncogenes: first, where the worker comes into contact with massive amounts of oncogene DNA material; and second, where work involves the deliberate and highly efficient production of oncogene proteins in bacterial cells. Now in both these cases the natural reaction of molecular biologists would be to assure us that a problem of occupational safety does not arise.[27] They would argue that oncogene DNA or bacteria synthesising oncogene proteins are unlikely to enter humans in the first place, and that even if they were to get in, the oncogene DNA and the synthesising bacteria would not establish themselves in the new environment because of selective pressures against them. To add to this, molecular biologists assure us that even if oncogene DNA and the synthesising bacteria were to establish themselves, no harm would ensue because of a whole range of in-built protective measures, such as nucleases in the gut, protein breakdown, barriers to protein absorption in the gut, the immune system, and so on.

To be sure, the human organism has a great range of protective mechanisms to guard against damage by foreign organisms and

materials. No doubt in many situations these mechanisms come into play and protect the worker who is engaged in the manipulation of hazardous materials. But in the last few decades we have come a long way in our attitudes towards the safety of workers. A reliance on unspecified, in-built bodily mechanisms is no longer adequate. In general, in the industrial relations arena it is now well recognised that occupational hazards have to be both pinpointed and counteracted. It is no longer acceptable to adopt a *laissez faire* approach, where the potential occupational problems are left ill-defined and the worker is thereby left poorly protected.

We should ensure that recombinant DNA safety complies with these general trends guiding occupational safety procedures. Hence, we should no longer be satisifed with theoretical arguments and counter-arguments on what is likely to happen if a worker comes to be infected with potentially hazardous materials arising from work with oncogenes. Many of the unanswered questions can now be approached experimentally. In the interest of occupational safety, it is important that theoretical discussions and assurances give way to a new experimental program of recombinant DNA risk assessment, focused primarily on dangers pertaining to the manipulation of oncogenes.

Below I will outline a few general principles relating to such a new program of risk assessment, but first I would like to point out why general assurances about the safety of recombinant DNA procedures do not extend to oncogenes. In the case of oncogenes, the occupational risk involved is cancer, a disease which is known to have an extremely long incubation period. By contrast, our laboratory experience with oncogenes commenced only in the last few years, and even the work with cancer viruses or retroviruses goes back only to the 1970s. So the argument that recombinant DNA work has been conducted in thousands of laboratories around the world without anything going wrong cannot provide any assurance of safety when we are dealing with oncogenes.[28]

Secondly, the past recombinant DNA risk assessment program of the NIH is often used as a supplementary line of argument for the safety of recombinant DNA procedures. I have summarised this risk assessment program above, and it can be seen that, with the possible exception of the retrovirus study of Martin, none of this risk assessment work is relevant to the safety appraisal of oncogenes. About Martin's study, there is not a great deal we can say. This work has not been published, and hence is not available for scientific discussion and criticism.

To emphasise, the manipulation of oncogenes is a totally new development in molecular biology. It is a research endeavour that started only in 1980, just at the time when the NIH sponsored risk

assessment program was being completed. The oncogene research field literally did not exist in the period before 1980.[29] Indeed, the initiation of this research, as well as its current rapid progress, have been posssible only because of the relaxation of restrictions on recombinant DNA work in 1980.

It will be recalled that before 1975 bacterial cloning in general was technically impossible. Then, between 1975 and 1980, there were many restrictions on recombinant DNA manipulations. In January 1980 many of these restrictions were lifted, and since then the cloning of oncogenes has been allowed under ordinary laboratory conditions, often called P1.[30] So, by 1980 two sets of obstacles to the manipulation of oncogenes had been removed — the technical ones as well as the regulatory ones. At that stage the cloning of oncogenes could commence, and this led directly to a great range of findings about the nature, origins and the mode of action of oncogenes. Today this area is pressing ahead, and risk assessment of oncogenes has been bypassed.

Thus, in contrast to many areas of research employing the recombinant DNA technology, neither day-to-day laboratory experience, nor risk assessment studies can provide us with an assurance of safety for oncogene research. In other words, work with oncogenes has certainly not been demonstrated to be safe. Quite to the contrary, as I have shown in earlier sections, there are several indications of potential occupational hazards which arise from the experimental findings of oncogene research itself. In my view, these conditions should bring about the replacement of the current haphazard way of talking about oncogene risks, with a systematic experimental program of risk assessment. Such a new risk assessment program would put us in a far better position to know where the hazards of oncogene manipulation lie. Suitable protection against these hazards could then be designed for those workers who are involved in the manipulation of oncogenes, be they in research laboratories or in commercial enterprise. This will set oncogene research and its commercial exploitation on a proper footing, without having to be inhibited by occupational problems occuring at a later stage.

Where might a new, experimental program of oncogene risk assessment begin? One reasonable approach would be to investigate the hazards associated with purified, concentrated oncogene DNA. I have pointed out that the joint action of the oncogenes *ras* and *myc* is able to convert normal cells growing in culture to the cancerous state. A useful starting point would therefore be to carry out a series of risk assessment experiments to determine whether such an oncogene combination also brings about cancer in living organisms.

The underlying principle of this approach would be to try out various combinations of oncogenes, use them in several concentrations and genetical constructs, and inject them into a variety of animals; for example, into so-called 'nude' mice lacking an efficient immune system, into new-born hamsters, chickens and so on. The explicit objective of such a program should be the achievement of tumour induction in the experimental animals by means of the introduction of oncogene DNA. I have no doubt that with some of the oncogene-animal combinations to be tried, tumour induction will be achieved. Once such a positive result is obtained, further experiments should be conducted to determine what factors can be relied upon to provide protection against tumour production in the organism. For example, let us assume that the injection of certain oncogene DNA leads to cancer in nude mice but not in normal mice. In such a case we would be relying on a well-functioning immune system to provide protection.

At that stage the discussion of oncogene-related occupational hazards can move to the industrial relations arena. It is in this forum that negotiations will have to take place to determine whether a well-functioning immune system is an acceptable line of defence for workers who are engaged in oncogene manipulations, or alternatively, whether physical protective measures have to be introduced into the workplace to provide more reliable protection. Similarly, we might find on the basis of animal risk assessment experiments that the injection of oncogenes is more likely to yield tumours than the ingestion of oncogene material. Again, such findings need to be considered in an occupational safety forum and appropriate protective responses devised.

What I am suggesting is that a guiding principle of the new oncogene risk assessment program should be to push the system to the limit so that a positive outcome, that is cancer induction, is achieved. With the hazardous factors of cancer production defined in this way, it will then be possible to work backwards to determine which laboratory manipulations are safe and which are not. On this basis steps can then be taken to ensure that the work environment is safe for all those who are engaged in oncogene manipulations. It is apparent that such a program of risk assessment will involve both scientific experimentation and negotiation in the industrial safety sphere.

CONCLUSION

In conclusion, it should also be said that even when we obtain experimental answers to the concerns I have raised here, this will not be adequate with regard to the safety of oncogene manipulations in general. A suitable program of oncogene risk assessment must be

ongoing, so that it evolves in step with the development of the oncogene research front. Only this will ensure that workers engaged in recombinant DNA based manipulations can be assured of a safe working environment, regardless of whether they are engaged in research *per se* or in its commercialisation.

Finally, I should also point out that in order to initiate a risk assessment program such as I have outlined above, a political decision at government level will be required. Who should sponsor such a new program? Likely candidates would be the various bodies around the world responsible for drafting recombinant DNA guidelines and ensuring the compliance of workers with them. Such bodies are the Recombinant DNA Advisory Committee (RAC) in the United States, the Health and Safety Executive in Britain, the Recombinant DNA Monitoring Committee (RDMC) in Australia and the Biologische Sicherheitskommission in West Germany. Until now these authorities have been rather reluctant to set up new risk assessment programs, since they have been assured by scientists over the years that the recombinant DNA technology is free from hazards. However, as we have seen, occupational problems have recently arisen amongst molecular biologists. It is to be hoped that these unfortunate circumstances will provide the impetus for establishing a new risk assessment program which focuses on the potential hazards involved in cancer research and which is based on the guiding principles outlined in this paper.

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24. For the sake of simplicity I have concentrated here on the effect of oncogene DNA *per se.* More recent work, particularly that conducted by Adams, Cory and their colleagues at the Walter and Eliza Hall Institute in Melbourne, shows that when certain genetic control elements (called enhancers) are linked to oncogenes, the combined sequence invariably leads to cancer in animals when embryos are injected with such combined sequences. These research findings, though exciting with regard to advances in the field, nevertheless point to additional safety problems for those who manipulate oncogene material. The relevant reference is J.M. Adams, A.W. Haris, C.A. Pinkert, L.M. Corcoran, W.S. Alexader, S. Cory, R.D. Palmiter and R.L. Brinster, 'The c-*myc* oncogene driven by

immunoglobulin enhancers induces lymphoid malignancy in transgenic mice', *Nature,* 318, December 1985, pp. 533-8.

25. J.A. Lautenberger, D. Court and T.S. Papas, 'High level expression in *E.coli* of the carboxy-terminal sequences of the avian myelocytomatosis virus (MC29) v-*myc* protein', *Gene,* 23, 1983, pp. 75-84; J.A. Lautenberger, L. Ulsh, T.Y. Shih and T.S. Papas, 'High level expression in *E.coli* of enzymatically active Harvey Sarcoma virus p21*ras* protein', *Science,* 221, 1983, pp. 858-60.
26. Workshop on Recombinant DNA Risk Assessment, Pasadena, California, *op. cit.,* note 12.
27. The various lines of argument are depicted in both the editorial comments and the documents found in Watson and Tooze, *op. cit.,* note 1.
28. Indeed, as was noted before, it was reported recently that five molecular biologists who worked on cancer research at the Pasteur Institute became ill with cancer at the same time. See notes 3 and 4 above.
29. J. Michael Bishop, 'Oncogenes', *Scientific American,* 246, March 1982, pp. 69-78.
30. Department of Health, Education and Welfare, 'Guidelines for reseach involving recombinant DNA molecules', *Federal Register,* 45 , 20, 1980, pp. 6732-8.