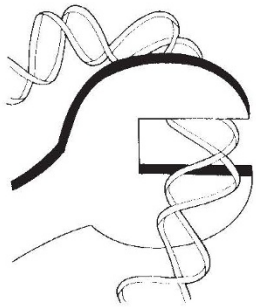

**LAST WEEK, the British trade union, the Association of Scientific, Technical, and Managerial Staffs (ASTMS), called the first public debate in Britain on the potential hazards of genetic manipulation. In the end there was little debate, which may indicate the level of public understanding of the question, but there were stimulating contributions from the platform. Here we reproduce shortened versions of the talks of Sydney Brenner, director-designate of the Medical Research Council's unit of molecular biology at Cambridge, and Jonathan King, Professor of Biology at the Massachusetts Institute of Technology. On a following page Eleanor Lawrence disentangles the threads of the biology involved, for the meeting blurred the distinction between genetic manipulation proper (using restriction enzymes *in vitro*) and other work (such as the investigation of dangerous pathogens, or recombination in natural systems). Finally, an ASTMS officer explains her union's plans to radicalise university research laboratories in Britain.**
**TODAY Britain's Genetic Manipulation Advisory Group (GMAG) is considering whether to adopt a new set of principles for assessing the hazards of individual experiments, much more precise than the 'rule of thumb' phylogenetic system so far adopted in the UK, the US, and elsewhere. Sydney Brenner was its inventor.**
**NEXT WEEK, if GMAG adopts the new guideline, *Nature* will publish a condensed version of them.**

# Six months in category four

**By Sydney Brenner**

I've been associated with this debate almost from its inception; and I can say that I have given a considerable amount of my time—perhaps four years of my life—to it, and certainly something like ten shelves in my office to the paper that has flowed out of the discussions. These discussions have been very extensive. It will be impossible here to go into all of the details of the subject. But one must look at the historical constraints under which the subject was approached.

Interest in the subject of 'genetic engineering' or 'genetic manipulation' was first aroused by a letter written by some Americans—Paul Berg and others—requesting a moratorium on this research. I must tell you that there was an immediate response in this country. I think that whereas the moratorium was enforced in this country, it was only treated as a voluntary matter in other countries. As an employee of the Medical Research Council (MRC) I received a letter at the time, from the then head of the organisation, instructing me to obey the moratorium. Of course it was quite easy to obey because we weren't doing experiments.

The Ashby Committee in the UK, followed by meetings at Asilomar, which was international, followed by the Williams working party, resulted in the institution of the Genetic Manipulation Advisory Group (GMAG). And I think that it is a unique institution in the world, in that it involves formally the participation of representatives of organisations who are not scientists. And insofar as the trades unions are part of the public, one has good public input.

Now why have we had this very elaborate organisation, GMAG? I think it is very important to understand why this particular area has been singled out for very special attention. It has been singled out for special attention because of the statement made very early that there were particular dangers associated with genetic manipulation—that is, risks that were so particular, and potentially so great, that people had better start to take special action about them.

"We 'genetic manipulators' question why this area has been singled out."

That created the historical background for why we have a GMAG for genetic manipulation. But there are lots of other things you can do in laboratories over which there is no control at all. Among we 'genetic manipulators' (if such a profession exists) there is a questioning of why this area has been singled out. It is the perception of people in the field that right next door there are people who do much worse things—you know, with the fags hanging out of the mouth, and a cup of tea, doing it any old way they like.

Now I think this is quite important, because one should desperately avoid the situation that one branch of science is singled out for the delivery of social punishment. Now I don't want to say this has happened, but I do want to emphasise that this is a kind of connection between science and society that we must avoid: that if scientists have been bad boys, as many people think—science *is* being questioned—then the genetic manipulators can so to speak carry the can and get six months in category four. That is a psychological situation that must be avoided.

We must begin to ask new questions about this whole area of research. One has heard the statement made this morning that a researcher can put antibiotic resistance into *Shigella sonnei* with no control; and you have to ask why isn't anybody controlling him? No one's controlling him because he is using natural mechanisms. That is, he's using the mechanisms used in nature to generate new strains—mutation, recombination, even perhaps genes that jump around from one piece of DNA to another; all he is applying to these mechanisms is special selection. He is fishing out of nature events that may be extremely rare and enriching them in a laboratory. His technology is that of enrichment. He creates by his techniques a local high concentration of such elements, of which there are enormous numbers, that lie all over the place.

What a genetic manipulator does is to do things *in vitro*. In theory, if you could do genetic manipulation by avoiding the use of test tubes then in fact you would be doing something that was a natural mechanism, and so in theory you might argue that you could escape from the GMAG regulations. I'm not offering that as a possibility, but I just want you to realise that the difference between genetic manipulation and other biology as understood by GMAG is that it is a sort of 'confined area' of genetic construction. And it is clear that you can make genetic constructions in organisms with natural mechanisms.

And so work on recombinant influenza viruses, work on recombinant bacteria, the transfer of promiscuous plasmids from one bacterium to another, that goes on, but doing the same work—indeed the identical experiment could be formulated—with a restriction enzyme would put you under the GMAG regulations. That is a paradoxical situation that we have to look into.

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Why does one have to look into this? Because of the question of what constitutes a risk. There are now moves in the United States to change the so-called 'guidelines' (which may be looked on by some as attempts to amend the Ten Commandments); but the question is what are the grounds for these amendments? Now of course there is the important ground that we have new knowledge, but I think there is another ground which should be honestly stated: namely, that the risk analysis was not properly done. (This is my personal opinion). Now why wasn't it properly done?

First, there are things we can actually say are dangerous. It is a remarkable thing there are natural objects we can say are risky. Smallpox virus is risky. A lot of bacteria are risky. The people who work with them know they are risky, and they will therefore take precautions. You don't play games with smallpox. No one can say it is a fundamental belief of his that smallpox isn't dangerous. One can convince him very quickly it's dangerous. So there is immediate feedback to the workers involved.

So with these things there is no problem in declaring what is dangerous. We have—if you like—knowledge about that. We know from historical, clinical, and epidemiological evidence that certain things will knock you off with a high probability. And there seems to me to be no question that those should be declared as such, and if people are fools enough not to accept control on such work, then we will see events such as we have seen in the past—not only in this country but in other countries as well.

There are 5,000 recorded cases of laboratory infection in the United States, and some of them—with *rickettsia*—had fatal consequences. There's no doubt about this. I think it's on this sort of evidence that we have to rely to judge the effectiveness of physical containment. The experiments have been done for us in the past—alas they should not have been done as experiments, but they are there, and we have to rely on that information.

But how are we to assess the potential and certainly the conjectural risks? Who will say what is dangerous? The difficulty here in doing a risk assessment is that we are in a field where we are dealing not with nuclear reactors, not with toxic substances, but with self-replicating biological entities. We are far away from questions of linear dosage. In most of the other cases, chemical and other substances, one can make calculations quite clearly which are based on linear dosage relations. You know what the toxic dose is, or one can do experiments to establish it or estimate it quite accurately, and therefore you can make conditions to prevent that toxic dose from reaching the workers and the public at large.

The trouble with the creation—or if I could call it the enhancement—of organisms is that they could depend very largely on their selective amplification. But that is the key thing. It is selective amplification that counts. Now let me make this clear what I mean. Years ago when I first started to travel in aeroplanes, with a very crude knowledge of physics and aerodynamics, I used to sit in those DC3s, and I had that marvellous vision with which I could look right into the aircraft engine; and I could see in all detail all the parts going round and round, the spinning of crankshafts and pistons and so on; and then I could actually see those hairline cracks developing. It used to worry me. I think many people look at genetic manipulation with that kind of internal vision. They see lying on the Petri dish the one horror bacterium, the one horror colony, the colony that is going to escape off that Petri dish and create global disaster.

I think that that feeling forms one of the most difficult hurdles to cross in trying to do objective risk assessment. And I believe that to be objective is very important. In the past in this field, we have had no more than the balance of example and counter-example. I have sat in on hundreds of arguments which have got into details that even mediaeval theologians could not have reached as to the total number of nucleotide base pairs that should be allowed under section B subsection A paragraph 1.2. And the situation has been, in my opinion, that people have been arguing about whether the leaf points up, or down, without actually realising on what branch they are standing. And it is a very important thing in this risk assessment—if we are to do it properly and responsibly—that we come to realise that this is a tree, that some branches are high, and some branches are low, and that it doesn't matter if the leaf points up or down if you are going to fall 130 feet. Of course it matters quite a lot if you are only a couple of inches from the ground because there won't be a leaf, but I'm just trying to say that the business of doing it by example and counter-example—that is, to offer an example scenario that you could in this way create a thing, without having any true estimate of the abundance of these examples and counter-examples—has seemed to me to have be-devilled this field right from the beginning.


And so I had a strong belief that what is necessary in companion with the control of the activities and the categorisation and so on is that it is necessary for all of us—I mean scientists and public participants—to get together and analyse the risks. The existing guidelines are wrong.

Now the guidelines are wrong in an interesting way. I think they are wrong because they have not been scaled with respect to each other. That's the first point. I think they are wrong because —and this I find particularly bad, as a biologist—because they seem to me to perpetrate biological myths—that is myths about the world—which don't exist any more. In large measure they resemble the view of biology which in fact underpins the guidelines in anti-vivisection: the concept that if you are cold blooded animals you don't feel pain, because the idea is that warm blood and emotion and pain all go together. (You can take frogs and maul them around as much as you like—but not cats and not dogs and not horses. That's an interesting biological classification.)

There is a strong scientific onus that we do *not* enshrine in legislation myths of biology. That seems to me to be an intellectual responsibility that we should share. But I think that there is another responsibility, which is the social one, and that is that we should not be imposing on a subsection of our scientific community and technicians and practitioners controls that appear to them—and objectively—completely extreme compared to what is going on in other fields.

Indeed, if one analyses this, a strong case can be made out that genetic manipulation is actually a method of attenuating dangerous things, and that it is not in itself intrinsically dangerous. In fact it can be argued very strongly that it is a way of containing things, of moving them away from organisms that are their targets, and locking them up in other organisms where they can do nothing. For myself, if there were some national emergency overnight that scientists had to get to work quickly on lassa fever, I would say that the first thing that we should do is clone it in bacteria. Let's clone it in bacteria, let's lock it up, because there it is rendered non-infectious. Then we

can work with lassa fever virus sequences safely in bacteria. (Let me just say that I think lassa fever virus cloning in bacteria is a big no-no experiment, both here and in the United States, and it would take the direst national emergency to make me work with lassa fever virus, and I'd be very, very careful myself!)

But this is a paradox of the whole field—I put it to you—it sounds awful, but I think I must put it as strongly as that—I would work with the lassa fever virus in *E. coli* any day. I'd consider that to be my best guarantee of safety.

I think you must ponder these things because at first sight they appear totally paradoxical. That is because we have not thought out the hazards directly. I think we have not solved all the problems, and I think there is an enormous amount of work that still remains to be done.❞

# New diseases in new niches

**By Jonathan King**

❝ Recombinant DNA certainly represents a major breakthrough in our ability to study the organisation of the genetic material of higher organisms; and I should say that from the research point of view recombinant DNA technology can be employed safely. Although in order to employ it safely you have to assess very carefully what's dangerous about it. But perhaps more relevant here is the new production technology, technology that will be used to manufacture commodities for sale. The transformation from research tools to production technology has proceeded far more rapidly than many scientists envisioned. Within a year or two in the United States Eli Lilly corporation expects to be producing human insulin through the growth of thousands of gallons of *Escherichia coli* containing human DNA sequences spliced into a bacterial plasmid.

Now the deployment of new production technologies has more often than not been associated with the generation of unfortunate side effects on the health and welfare of the human population—most notably those employed at the point of production. I have here a few historical examples. For example the mechanisation of cotton textile manufacture resulted in a drastic increase in damage to the respiratory tract of the operatives (byssinosis or brown lung). Developments in the German chemical industry—such as the synthesis of the aniline dyes which were used to colour the textiles—entailed the production of potent bladder carcinigens—4-aminobiphenyl and $\beta$-naphthylamine.

Most of us can be reasonably assured that most of those chemical carcinogens that are already out there through previous mishandling will not reproduce and increase themselves in the environment. The risk is finite. In the case of bacteria we do have to worry that these organisms—or at least the genes that are linked to the plasmids within these bacteria—will move through the ecosystem, transfer for example from the debilitated strains to wild strains of bacteria, and get into strains which perhaps are well-adapted in a particular niche out there. And then we won't be able to clean them up, for you can't remove, for example, *E. coli* from the ecosystem. It is an intimate part of mammalian life.

Now at this point I wish to clarify and punctuate a very crucial aspect of risk assessment. In trying to assess hazard we must consider what would be the properties, for example, of a wild strain of *E. coli*—even an epidemic strain of *E. coli*—expressing, for example, the human gene for insulin. Now some in the audience will heatedly reply—or they would if I were at home—"but they'll never get into wild strains, they're in debilitated strains, you've got nothing to worry about, you're raising a false spectre". This is of course putting the cart before the horse. The only way that hybrid DNA will be contained, is if people understand that if it is *not* contained there may be problems.

Thus in assessing the risk of cotton dust, we do not examine the effect of cotton fibres on human skin; we examine the effect of cotton fibres on human lungs. Of course, manufacturers in the industry often say "no that's wrong, because the cotton fibres will never get into the workers' lungs". But we know that that it is only if people understand acutely what will happen if those fibres *do* get inside the lung, that action is taken. And knowledge in the past has not been sufficient, it's taken much more action than knowledge.

I must ask: where have infectious diseases come from? After all if I'm going to make a feasible case that there is something to worry about in generating a new human disease, I'm behoven to explore the question of the generation of old ones.

The virulent form of *cholera Vibrio* infection, with characteristic rice-water stools, was first reported in the highly densely populated and unsanitary city of Calcutta in 1817. From there it was carried by the British navy to the newly emerging industrial areas in the north-west of England. Manchester in this period was rapidly converting from cottage production of cotton textiles to full-scale factory production. The workers needed to man the mills were either forced off agricultural holdings or one way or another brought into the city, and essentially forced to live in housing not of their own design. The nature of this housing is quite well documented—miserably crowded, very little light or ventilation, no sanitation, no proper water supply, no means of disposing of waste, thus garbage and excrement polluting the waters used for drinking and washing and food preparation.

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Cholera thrived in these industrial districts because these organisms multiply in the intestine, where they elaborate a toxin; and this toxin binds and penetrates the cells of the intestine, and inactivates a protein of the intestinal cells which is needed in protein synthesis. The organism however goes out in the faeces, and if you live in an area with a contaminated water supply and you drink that stuff—boom—you get cholera.

The growth of textile manufacture in the north of England, and also in the midlands, gave rise to many other niches. One of them was damaged lungs from cotton fibres, particularly among operatives of the carding and combing room, where the cotton is taken from the boll to the fibre. These individuals were unusually susceptible to tuberculosis and pneumonia infections, since with the primary barrier of the lung and respiratory tract broken, these organisms move down the respiratory tree and eventually get down to the alveoli of the lung, when you have profound tuberculosis and pneumonia.

Given the conditions that they lived in at home, where there was very very close person-to-person contact, contaminated food, no pasteurisation, etc, there were once again created special conditions for these organisms to

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