which is a possible vehicle for inserting genes into *E. coli* for cloning, also took longer than anticipated. Until such strains are available, the Asilomar guidelines specify that the voluntary moratorium should be maintained for many kinds of experiments. Consequently, most planned experiments have effectively been under an embargo for 18 months.

It is in that difficult situation that the NIH advisory committee has been trying to write acceptable regulations from the Asilomar guidelines. And it has also been working in an atmosphere charged with suspicion and unconfirmed rumours that embargo-breaking experiments are being carried out clandestinely. In short, the committee has been under considerable pressure to come up with regulations which would allow some of the work to be resumed, and which would at least remove the uncertainty. As one committee member said, if the committee failed to draft regulations at its December meeting, "the dam would be likely to break".

Thus, early in July, a subcommittee under the chairmanship of David S. Hogness, of Stanford University, drafted a set of regulations for consideration by the full committee at a meeting held in Woods Hole later that month. The Hogness version offered some stringent controls which, in most respects, conformed to the Asilomar guidelines, but which were weakened in a few key places at the Woods Hole meeting. It was those changes which have caused the committee most of its problems, and which led to the meeting in La Jolla.

The Woods Hole draft was to have been the committee's final report, but when it was circulated around the scientific community, it encountered so much criticism—including adverse reaction from two committee members, Roy Curtiss III of the University of Alabama, and Stanley Falkow of the University of Washington (who was not present at the Woods Hole meeting) —that it was never published in final form. Instead, the committee chairman, DeWitt Stetten, Deputy NIH Director for Science, appointed another subcommittee under the chairmanship of Elizabeth Kutter of Evergreen State College, Washington, to draft an alternative set of regulations for the committee to consider. The Kutter draft, which was completed in November, was in some respects more restrictive than either the Hogness or Woods Hole versions.

Among the criticisms levelled at the Woods Hole draft was a statement signed by some 50 participants at a conference held in August at Cold Spring Harbor, who complained that it "appears to lower substantially the safety standards set and accepted by the scientific community as represented by the meeting at Asilomar". And another particularly influential critic of the draft was Paul Berg, who wrote in a letter to Stetten that the restrictions proposed for some types of experiments are "marginal and inadequate considering the risks the document itself concedes"; he suggested that in one particular case, the regulations "are very likely to draw the charge of self-serving tokenism". Some critics took the opposite view, however, suggesting that the Woods Hole regulations were so strict as to constitute unwarranted infringement on academic freedom.

Thus the committee met here in a situation which had all the ingredients of a possible show-down, but it nevertheless conducted its business with little animosity. The entire committee turned up (15 members including the chairman), together with six special consultants who included Berg and Maxine Singer, a virologist from the NIH who was an organiser of the Asilomar conference.

On the first day of the meeting, the committee approved, by a series of close votes, restrictions on some types of experiment which differed little from the Woods Hole draft, and which would inevitably have drawn considerable criticism for being too lax. But on the second day, it went back over some of those recommendations and, by equally close votes, tightened the regulations considerably, so that in some instances they are even more stringent than the Asilomar guidelines.

It is difficult to know exactly what made a few committee members change their votes, but one member indicated privately that after considering the matter carefully, he decided that in cases where there is disagreement, the committee should, as a matter of policy, adopt the more stringent option. It is always possible to lower the restrictions at a later date, he suggested, if evidence becomes available to suggest that the risks have been overstated. Another consideration was the practical one that if the committee adopted regulations which meet with criticisms for being too lax, then it was entirely possible that the matter could be taken out of the hands of scientists, and the technique regulated by legislation—a possibility which clearly bothers many people because it smacks of political infringement on academic freedom.

The committee's move to adopt strict regulations was made easier by an important development. A week or two before the meeting, Roy Curtiss, whose laboratory has been working full-time since the Asilomar conference on the problem of constructing a genetically crippled strain of the *E. coli* K12 bacterium, finally produced a strain which seems to meet all the requirements. He has tested it in rats, and found that it does not survive in the intestine, and after some more tests are completed, he believes that it will fit the bill. Similarly, at least two strains of bacteriophage lambda have passed

Figuring the risk

THE hazards associated with cloning recombinant DNA molecules can only be speculated about, since there is no experimental evidence to prove or deny that they exist. Thus the NIH advisory committee was attempting to write regulations based largely on guesswork about the likelihood that, for example, a bacterium or virus bearing genes transplanted from another organism could pose a danger to animals or plants — a situation, as DeWitt Stetten, the committee chairman points out, "in which Lloyd's of London refuses to write insurance".

The committee therefore unanimously approved a resolution urging the NIH to sponsor a potentially hazardous experiment, in maximum physical containment facilities, to gain some data on the likely extent of the risks. The experiment, which was suggested by Sydney Brenner of the MRC Laboratory for Molecular Laboratory, Cambridge, would involve splicing genes from a polyoma virus (a mouse tumour virus) into a bacterial plasmid, cloning the recombinant molecule in *E. coli*, and infecting young mice with the modified bacterium.

The idea would be to monitor the mouse's serum to determine whether antibodies to polyoma virus are formed. If they are, it would indicate that the transplanted genes are working, and are being transmitted into the animals' blood stream, in which case there is a real danger that many of the postulated risks exist. If no serum antibodies are formed, it would indicate that at least in this case, the genes are not being expressed in the animal's system, which would suggest that some of postulated hazards are less plausible. There is a danger, however, that such a negative result could be over-interpreted as suggesting that recombinant experiments are inherently safe.

If the experiment is carried out, it would be performed in maximum containment facilities at the NIH, which easily meet the P4 requirements, and it would be conducted by an eminent virologist.