

they are interested in a variety of scientific and technical help. Iran, for example, is seeking help in agriculture, fertilizer production, manpower training, housing, urban development, remote sensing, seismic studies, geological and mineral surveys, oceanography, and even radioastronomy. Why radioastronomy? One theory is that the Iranians figure if they become a world leader in some such esoteric field, it will be easier to interest talented Iranians who are now working abroad in returning home.

The Saudis have expressed great interest in desalination, solar energy, irrigation techniques, modular housing, educational

technology, and hydrocarbon technology, among other fields. Both countries are interested in nuclear technology, the Iranians more immediately, the Saudis possibly in conjunction with a large-scale desalination plant. And both are pursuing various industrial technologies with the private sector and in a number of different countries.

One widely touted possibility—that American know-how and Middle East oil money might unite to develop the Third World—has not yet blossomed. As Lewis Bowden, the Treasury Department's deputy for Saudi affairs, put it: "There has

been a good deal of talk without much substance of what people are calling triangular investment. What they have in mind here is that Saudi Arabia or Kuwait or Iran, a capital surplus country at the present time, would put capital into another developing country—Egypt is usually mentioned in this respect. The third part of the triangle would be managerial know-how from a developed country like the United States or Germany or France. So far as I know, except in the private sector, there have been no such combinations and we do not really know what the future will hold in that respect."—PHILIP M. BOFFEY

Recombinant DNA: NIH Group Stirs Storm by Drafting Laxer Rules

A flurry of objections has been touched off in the biological research community by a National Institutes of Health committee's first attempt to draft the terms under which work may proceed on a potentially revolutionary but currently embargoed technique of genetic manipulation. Some think the proposed rules will impede research by their unnecessary strictness, but the majority of objections, including a petition signed by 50 biologists, hold that the NIH committee has set safety standards considerably laxer than those agreed upon by the international conference held at Asilomar to discuss how the new technique should be controlled (*Science*, 14 March 1975).

The technique, in brief, involves the use of recently discovered enzymes to rearrange the genetic material of living organisms in novel combinations which may never before have occurred in nature. The reason for the embargo is that the recombinant DNA molecules, as they are called, might escape from the laboratory with consequences which cannot be foretold but which, at the worst imagining, include the generation of novel and uncontrollable epidemics.

The technique will doubtless procure several Nobel prizes for those skilled and lucky enough to bring home first fruits, not to say many practical benefits in medicine, industry, and agriculture. There is considerable impatience in many laboratories for the NIH to complete its guidelines so that

work can begin. The NIH committee* is working in a charged atmosphere in which suspicion is rampant and in which everyone has heard rumors that embargoed experiments have been clandestinely performed at certain laboratories. (*Science* could confirm none of these rumors; Paul Berg of Stanford University, the guiding spirit of the Asilomar conference, says he has seen no published experiment which contravenes the principles adopted there.)

The root cause of the objections attracted by the committee's first draft should probably be sought not in any lack of goodwill on the part of the committee—although some charges of conflict of interest are being voiced—but rather in the extraordinary difficulty of translating the general principles laid down at Asilomar into practical guidelines that everyone can live with.

Because of the way it has reacted to the criticism, however, the NIH committee has woven itself into a procedural tangle which may not be resolved without some internal friction. Essentially what has hap-

pened is that a subcommittee under David S. Hogness of Stanford University drafted a set of guidelines which were substantially weakened during a July meeting at Woods Hole attended by 8 of the committee's 12 members. The weakened, Woods Hole version attracted serious criticism on that account from Berg and from the signatories of a petition organized by Richard Goldstein of the Harvard Medical School and Harrison Echols of the University of California at Berkeley.

In response to the criticisms, committee chairman Dewitt Stetten, NIH Deputy Director for Science, asked Elizabeth Kutter of Evergreen State College in Olympia, Washington, to form a new subcommittee and propose alternative guidelines. The Kutter guidelines are due to be completed and sent to committee members this week, and will probably be more stringent than either the original Hogness guidelines or the Woods Hole version. According to committee secretary William J. Gartland, even the Hogness version does not adequately reflect the tone of caution implicit in the Asilomar conference's recommendations. The committee will discuss the Kutter guidelines at its meeting in San Diego early next month, but discussion may be complicated because of the irritation felt by some members at the way the Woods Hole version has apparently been abandoned.

What the Woods Hole guidelines essentially do is to set up categories of physical and biological containment and assign combinations of the two to the various types of recombinant DNA experiments at present envisaged. There are four levels of physical containment, named P1 to P4 in ascending order of strictness, and three levels of biological containment, designated EK1 to EK3 because it is assumed that most experiments will take place in the common laboratory strain K12 of the human gut bacterium *Escherichia coli*.

*Members of the committee, known as the Recombinant DNA Molecule Program Advisory Committee, are as follows: DeWitt Stetten, NIH (chairman); Edward A. Adelberg, Yale; Ernest H. Y. Chu, University of Michigan; Roy Curtiss, University of Alabama; James E. Darnell, Rockefeller University; Stanley Falkow, University of Washington, Seattle; Donald R. Helinski, University of California, San Diego; David S. Hogness, Stanford University; John W. Littlefield, Johns Hopkins Hospital; Wallace P. Rowe, NIH; Jane K. Setlow, Brookhaven National Laboratory; Wacław Szybalski, University of Wisconsin; Charles A. Thomas, Harvard Medical School; Elizabeth M. Kutter, Evergreen State College; John Spizizen, Scripps.

The Right to Free Inquiry

What degree of restriction on the recombinant DNA technique can reasonably be accepted without infringing the right to free inquiry? A suggestion that no such absolute right exists has been put forward by Robert Sinsheimer of Caltech. At the Asilomar conference, he noted in a recent lecture to the Genetics Society of America, "there was no sustained discussion of ancillary issues such as the absolute right of free enquiry claimed quite vigorously by some of the participants. . . . To impose any limit upon freedom of inquiry is especially bitter for the scientist whose life is one of inquiry; but science has become too potent. It is no longer enough to wave the flag of Galileo.

"Rights are not found in nature. Rights are conferred within a human society and for each there is expected a corresponding responsibility. . . . Would we wish to claim the right of individual scientists to be free to create novel self-perpetuating organisms likely to spread about the planet in an uncontrollable manner for better or worse? I think not. "This does not mean we cannot advance our science or that we must doubt its ultimate beneficence. It simply means that we must be able to look as what we do in a mature way. . . .

"It is difficult for a scientist to conceive that there are certain matters best left unknown, at least for a time. But science is the major organ of inquiry for a society—and perhaps a society, like an organism, must follow a developmental program in which the genetic information is revealed in an orderly sequence."

At the risk of some slight distortion, these safety levels may be summarized as follows:

P1: Use standard microbiological techniques.

P2: Same as P1 but hang a Keep Out notice on the door while the experiment is in progress.

P3: Same as P2 but put the lab under negative air pressure, or if you can't manage that, at least use negative pressure cabinets.

P4: Same as for handling really dangerous agents—air locks, negative pressure, change clothes and shower, and so forth.

The biological containment levels are intended to satisfy the Asilomar requirement that the organisms used in possibly hazardous experiments be rendered demonstrably incapable of surviving outside the laboratory environment. Again at the risk of simplification, the Woods Hole guidelines stipulate the following three levels:

EK1: Just use the standard laboratory version of *E. coli* K12 as the host for your recombinant DNA molecule, and use *E. coli*'s standard virus or plasmids (independently replicating bacterial chromosomes) as the vector (that is, as the means of getting your molecule inside the bug).

EK2: Use strains of *E. coli* genetically altered so as to be *in theory* 10^6 times less likely to escape successfully from the lab than standard *E. coli* K12.

EK3: Same as EK2, except that someone has gotten around to actually confirming by empirical test that the disarmed

bug is indeed 10^6 times less likely to make a successful breakout.

One of the most unpredictably hazardous class of experiments made possible by the new technique is the so-called "shotgun" experiment, in which the whole DNA of an organism is chopped enzymatically into segments a few genes or so long, and inserted into bacteria for cloning. The most dangerous of all possible shotgun experiments, some people believe, is that involving the genetic complement of the organisms closest to man, such as other primates. Under the Woods Hole guidelines, shotgun experiments with all mammalian genomes could be carried out under conditions of P3 physical containment and EK2 biological containment. For warm-blooded animals other than mammals you could loose off your shotgun under conditions of P3 and EK1 or, if you didn't like that, with P2 and EK2 safety requirements instead. (The Asilomar guidelines specify the equivalent of P3 and EK3.) For cold-blooded and other lower animals, unless they are known pathogens, Woods Hole asks you to use P2 and EK1 (that is, completely standard laboratory techniques and materials, except for the Keep Out notice).

The original Hogness subcommittee guidelines are understood to be essentially the same as the Woods Hole version, except that various experiments were assigned stricter containment levels, and the "disarmed" *E. coli* cited in EK2 and EK3 were required to be 10^8 , not 10^6 , times less likely to survive outside the laboratory. Another change, according to Wacław

Szybalski of the University of Wisconsin, was to make things easier for people accustomed to using plasmids as their vectors rather than phages (bacterial viruses). Says Szybalski, in whose laboratory a "disarmed" phage has been constructed: "There are more people on the committee who have an investment in plasmids than in phages, which happen to be safer vectors, so the committee is a little opinion slanted toward making adjustment to plasmid standards."

The most influential critic of the Woods Hole guidelines is Paul Berg, chairman of the National Academy of Sciences committee that first called for the moratorium and the convening of the Asilomar conference 16 months ago (*Science*, 26 July 1974). The nature of Berg's criticisms is fairly widely known but the following account is unauthenticated because Berg believes it premature to discuss his views. Berg is said to believe that the Woods Hole version is much weaker than the Hogness draft which he regards as perfectly acceptable; that methods of physical containment are overrated because they are all vulnerable to human error; that even the P3 level of containment would reduce but not eliminate human exposure within and outside the laboratory; and that the only sensible way to avoid this leakiness is to enfeeble the host and vector organisms so greatly that even mistakes can't create potential tragedies.

Quite similar objections are raised by the 50 petitioners. They are concerned in general that the Woods Hole draft "appears to lower substantially the safety standards set and accepted by the scientific community as represented at the meeting at Asilomar." Specifically, they urge that the most hazardous experiments be postponed until experimental determination has been made of their risks. Second, the petitioners express concern at the P3 and EK2 conditions recommended for mammalian shotgun experiments; such experiments should take place only under P4 conditions until biological barriers of proved efficacy (EK3) are available.

Third, the petition raises questions about the composition of the NIH committee. There should be more members who have no direct interest in shotgun experiments, say the petitioners; there should be representation of the public at large; and the committee should span a broader range of scientific disciplines.

Goldstein, one of the organizers of the petition, is now preparing with two others a radical critique of the Woods Hole guidelines in which he argues that use of standard *E. coli* as a host organism is unsafe "in any size, shape or form." The

NIH committee envisages *E. coli* as the organism of choice because, through its having become a standard laboratory workhorse, more is known about its behavior than about that of any other bacterium. But the fact that *E. coli* infects man, argues Goldstein, that it easily becomes airborne and lodges in the throat, makes it a "reckless" choice and "ecologically unsuitable" as host to recombinant DNA molecules of potential hazard. (The committee's microbiology expert, Stanley Falkow of the University of Washington, Seattle, considers the K12 strain of *E. coli* to be enfeebled to the point of being relatively harmless, but even he believes that "we are ignorant in large part of the ecology of *E. coli* and of its plasmids and its phages.")

Because of the infectivity of *E. coli*, Goldstein says, the physical levels of containment recommended in the Woods Hole guidelines are "practically meaningless" except for the highest level, P4. *Escherichia coli* should be used as a host only for comparatively safe experiments until a new bacterial host is developed which cannot infect man, Goldstein contends.

Another critique of the Woods Hole guidelines is being prepared by the Genetics and Society group of Scientists and Engineers for Social and Political Action. A member of the SESPA group, Jonathan King of the Massachusetts Institute of Technology says that the function of the NIH committee, as presently constituted, "is to protect geneticists, not the public." Hogness, chairman of the subcommittee that wrote the original guidelines, is an active worker in the recombinant DNA field, which King likens to "having the chairman of General Motors write the specifications for safety belts."

Szybalski, a member of the Hogness subcommittee, agrees that there was a potential conflict of interest but defends Hogness by saying he acted with impartiality: "Hogness did an admirable job and tried to be fair, but he is very vulnerable to that criticism; I admire him for doing the job well and for his courage in taking it on," Szybalski says. Hogness rejects the charge of conflict of interest, saying that in the area he is working in, shotgun experiments with *Drosophila*, there is no disagreement he knows of on what the appropriate safety precautions should be.

The Hogness subcommittee has now been disbanded and the initiative at present seems to rest with the Kutter group. Who is Elizabeth Kutter? She became a member of the committee only after the July meeting, which she attended as an observer. Her name was proposed to the committee by Szybalski, who had met her at a conference in Canada. She was co-opted partly in

response to the committee's desire to have a layperson, or at least a semilayperson, as well as some one from a small college, among their ranks. Kutter in fact has a Ph.D. in biophysics and works with phages.

At a meeting in May Kutter suggested to the committee that she hold a session on constructing safer phages at the Cold Spring Harbor phage conference in August. Before the conference she expressed her concern about the Woods Hole guidelines to Goldstein and King in Boston. Her session at the phage meeting turned into a general criticism of the guidelines, and it was from this session that the Goldstein-Echols petition was set in motion.

Panicky Reaction

In response to this and maybe other criticisms, the NIH asked Kutter to draw up new guidelines, an action which has caused some distress among committee members. Szybalski regards it as a "terribly panicky reaction to criticism." All that was necessary was to revert to the Hogness draft, he says, since it was in fact the changes in the Hogness draft that the critics were objecting to. Committee chairman Stetten comments that in retrospect, "It is possible we did not react as judiciously as we might have, but there was an emotional and significant wave of criticism in some quarters against the Woods Hole draft."

Kutter's task has been made more difficult because of a report emanating from Goldstein (who says Kutter told him so) that the Woods Hole guidelines have been scrapped. "That made me climb the wall," says one committee member. According to Stetten, the NIH committee has not set the Woods Hole draft aside, but rather is "looking at it again." Kutter, however, is using the Hogness draft, not the Woods Hole version, as her basic text; the Woods Hole version, she says, "is not being put into effect."

The Kutter subcommittee, which met early this month, consists of herself, Falkow, and Joe Sambrook of Cold Spring Harbor. Sambrook is not a member of the committee but represented a subgroup on animal viruses working under Wallace Rowe of NIH. Kutter is taking input from a large number of sources, including Hogness, Berg, Joshua Lederberg of the Stanford University Medical Center, and the various letters received by the committee. Her goal, she says, is "to get together all the dissenting ideas and come up with compromises."

Several committee members, Stetten included, are anxious to prevent the committee becoming polarized into opposing camps. Given the paucity of data on which to make a decision, and the conflicting

pressures on the committee, it is not surprising that there should be a range of views. "We are being asked to set guidelines based upon hazards based upon accidents which have not yet happened. Even Lloyds of London is unwilling to write insurance on accidents for which there are no actuarial data," says Stetten.

Despite the darkness in which the committee is working, pressures are mounting for it to take a leap anyway. "If you keep everybody waiting, there is going to be stuff done on Saturday night," says committee member Jane K. Setlow of Brookhaven National Laboratory. "Many people I know have invested in P3 containment facilities and are being held up for lack of guidelines," notes Hogness. Stetten intends to produce a set of guidelines at next month's meeting. But the committee is in the unenviable position that however hard it tries, it is unlikely to make everyone happy.—NICHOLAS WADE.

RECENT DEATHS

Leslie O. Ashton, 83; professor emeritus of pediatrics, New York University; 2 September.

Fernando G. Bloedorn, 61; professor of therapeutic radiology, Tufts University; 6 September.

Oliver W. Burke, Jr., 65; president, Burke Research Company, Pompano Beach, Florida; 9 August.

Harold T. Cook, 71; former director, marketing research, U.S. Department of Agriculture; 13 August.

Lester R. Dragstedt, 81; professor emeritus of surgery, University of Chicago; 16 July.

Royce G. Kloeffler, 85; professor emeritus of electrical engineering, Kansas State University; 29 July.

Knut A. Krieger, 64; professor of chemistry, University of Pennsylvania; 19 July.

Charles L. Lazzell, 78; professor emeritus of chemistry, West Virginia University; 10 June.

Daniel J. Nelson, 49; assistant director, environmental sciences division, Oak Ridge National Laboratories; 16 August.

Edgar Stedman, 84; reader emeritus, biochemistry department, University of Edinburgh Medical School, Scotland; 8 May.

Perry R. Stout, 66; professor emeritus of soil science, University of California, Davis; 14 July.

Raymond W. Swift, 80; professor emeritus of animal nutrition, Pennsylvania State University; 11 July.