ment's environmental monitoring program "has convinced us that Mirex is one of the least hazardous pesticides in the environment today." Says Lee, "residues per se I don't think mean anything," and "I don't think anybody has determined what persistence means." He claims that the evidence of ill effects on aquatic life was derived under artificial conditions and that out in the field there is at least a thousandfold safety factor.

There continues to be disagreement on the ultimate threat the fire ant poses. Environmentalists claim they have just about reached their natural limits; Southerners claim that the ants, who favor a warm, moist clime, could spread as far west and north as California and New Jersey. Entomologists not employed at the USDA agree that total eradication of the ant (which is still the heart's desire of USDA) is a preposterous goal given the amount of money it would entail. They say, too, that persistent attacks on the pests have prevented them from settling into an ecological niche where the population would become stable and predictable. They believe the ant population is beginning to level off nonetheless and that ground applications of pesticide in areas where the ants come in contact with humans would be sufficient to keep the problem under control.

Biologist E. O. Wilson has said, "the fire ant control program in the South is the South Viet Nam of entomology." Another entomologist, William L. Brown of New York State College of Agriculture and Life Sciences, calls the aerial spraying program "absolute insanity." An EPA official says, somewhat hyperbolically, "There's been nothing like Mirex in the history of man . . . the government pouring stuff over 25 percent of a state's territory free of charge that is known to be toxic, and continuing in the face of great opposition."

An issue that has been sucked so deeply into the vortex of politics cannot readily be brought under control by facts alone; probably the emotion generated in a public that is becoming increasingly frightened by the loading of toxins into the environment has as much to do as anything else with closing down the Mirex program. Butler adds that without constant pressure from environmentalists and their efforts to stiffen spines at EPA, "this would have collapsed on the shoals of politics long ago." An EPA lawyer concurs: "We'd never do anything around here if it weren't for the environmentalists."

The question now is what to substitute for Mirex. Congress recently voted $400,000 to the Agricultural Research Service and $100,000 to EPA to work on this problem. USDA has looked over thousands of compounds and found nothing promising. The work that has generated the most interest is that directed by Earl Alley at Mississippi State University, who is seeking to develop a version of Mirex that will be less long-lived (it has a half-life of 12 years). Alley says the work was on the back burner for a while but now it's been moved to the front, and field tests are planned soon, using Mirex combined with amines that are supposed to make it more polar. Mirex is very nonpolar, which means it is nonwater soluble. Ideally, the new compound would degrade in a matter of days because it only takes about 4 days for the bait to become rancid and unattractive to ants. As for non-Mirex alternatives, the cupboard is now bare, but an EPA lawyer says he believes the free enterprise system will come up with something before long—"there's a lot of money in the fire ant market."

—CONSTANCE HOLDEN

Recombinant DNA: A Critic Questions the Right to Free Inquiry

When the issue of recombinant DNA came up last month before the Senate health subcommittee, the following exchange occurred between the senators and Robert Sinsheimer, chairman of the biology division at Caltech:

Kennedy: Do you agree that in terms of magnitude this is of as great significance as the splitting of the atom?

Sinsheimer: What this technology does is to make available to us the complete gene pool of evolution. We can take the genes of one organism and recombine them with those of others in any manner we wish. To my mind that is an accomplishment as significant as the splitting of the atom.

Schweiker: Are you saying that all that has gone before, we now have the power to change in some way—the evolutionary process?

Sinsheimer: Yes.

The senators did not follow up on the implications of the comparison they were drawing, but the analogy between nuclear energy and the recombinant DNA technique is one that Sinsheimer himself has raised. In a voice too gentle and well-mannered to receive much attention, he has been asking whether the scientist's claim of an absolute right to free inquiry should not sometimes be limited in the interests of society. Nuclear energy may yet turn out to be one such field that would better have remained forbidden territory. The recombinant DNA technique, he suggests, could prove to be another. "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," Sinsheimer said in a lecture last year to the Genetic Society of America.

With the notable exception of Erwin Chargaff of Columbia, Sinsheimer has stood virtually alone in his doubts about the wisdom of going ahead with the recombinant DNA technique, a method of genetic engineering which in essence allows each gene in an organism to be manipulated, whether for study or practical purposes. Most biologists believe that the work should proceed under appropriate safeguards. That approach has prevailed, and is embodied in the guidelines for research issued by the National Institutes of Health this June. Most of the public debate about the technique has revolved around what particular level of safeguards is appropriate, and public attention now rests on the next logical stage in the approach, that of ensuring that the NIH guidelines are followed by other government agencies and by industry (see box).

The approach of the NIH guidelines is a reasonable and responsible first step which has the full endorsement of those who first drew attention to the possible hazards of the technique, including biologists such as Paul Berg, Maxine Singer, David Baltimore, and Norton Zinder. How can Sinsheimer both differ from such eminent authorities and have a case worth making? The answer, perhaps, lies

Guidelines Extended but EPA Balks

The NIH guidelines governing research on recombinant DNA, however fine they may be, will prove of little value unless their writ is made to run beyond NIH and its grantees. At a half-day hearing held on 21 September by the Senate health subcommittee, chairman Edward Kennedy made clear that if industrial companies fail to comply with the NIH guidelines voluntarily, he will make them do so by law.

The subcommittee indicated no desire to make changes in the guidelines. Congress cannot legislate an appropriate answer in this matter; its proper role is to ensure public debate, Kennedy said.

General Electric, a company that is active in recombinant DNA research, refused to send a witness to the hearing, but a more cooperative attitude was evinced by the Pharmaceutical Manufacturers Association. PMA president Joseph Stetler told Kennedy that with some minor modifications, such as a lifting of the prohibition on production scale experiments, the drug industry "should and will accept the guidelines as an affirmative and constructive approach." According to Stetler, all major drug companies are interested in the technique but only six are actively engaged in recombinant DNA research, these being Hoffmann–La Roche, Upjohn, Eli Lilly, Smith Kline and French, Merck, and Miles Laboratories.

Comments on the NIH guidelines are being prepared by a PMA panel convened as a result of an industry-NIH meeting held this June. (The general industry sentiment at that meeting was that the guidelines were acceptable in principle, except insofar as they would render research results open to competitors, and that industry, being more safety conscious, would have less difficulty than universities in complying with them. "It's harder to destroy the world without people noticing what you're doing in an industrial lab than in an academic lab," observed a scientist from Merck.)

Another industrial aspect inquired into by the Senate health subcommittee was that of patents. A patent based on work by Stanley Cohen of Stanford and Herbert Boyer of the University of California has been applied for by the two universities. The application, which would cover only commercial use, not academic or industrial research, is apparently so broadly drawn that if granted in full it would include most uses of recombinant DNA. Kennedy expressed concern that work done under the patent might not be subject to the NIH guidelines. NIH director Donald Fredrickson confirmed that the NIH's existing patent agreements with the two universities gave them the first option to ownership of all inventions. But he said that the universities had indicated a willingness to modify their patent agreements on recombinant DNA in accordance with NIH's wishes, and that he intended to see that when the patent-holder licences the patent to other users the guidelines will be followed.

Will the NIH guidelines be followed by other government agencies? The National Science Foundation has announced its adoption of the guidelines, and the Department of Defense has said it would adopt them were it doing any research in the area. Senator Javits said at the hearing he would call the White House forthwith to find out why the Department of Agriculture had not yet announced its adherence. Fredrickson promised the subcommittee he would "make sure that the CIA is informed of the guidelines" and said he was "certain that all government agencies will shortly be under these guidelines." An interagency committee on the subject met in April but has not come together since.

One agency that has a possibly serious objection to the guidelines is the Environmental Protection Agency. An important but much criticized feature of the NIH guidelines is that they permit the human gut bacterium *Escherichia coli* to be used as a host for recombinant DNA molecules. EPA research director Wilson K. Talley told the Senate subcommittee that he disagreed with this principle. "We believe that recombinant DNA research should be performed on organisms which would be unable to live outside the laboratory environment and which are less ubiquitous than *E.coli*," Talley said.—N.W.

with the difference of perspective in which the two sides view the recombinant DNA technique. Those behind the guidelines approach see the problem as being one of how to take the next step in a way that will bring the most benefits to science and society while keeping the risks to a minimum. In Sinsheimer's view, the question is whether, in the light of what we know of history and of the process of evolution, it is prudent to take that step at all.

Sinsheimer is a member of the National Academy of Sciences and editor of its *Proceedings*. Cracking the unusual structure of the virus ϕX174 is one of his feats. He has not always been skeptical of the fruits of scientific progress. As those who disagree with him on recombinant DNA find frequent occasion to recall, he was once an ardent advocate of genetic engineering. In an article of 1970 he looked forward to the advent of human genetic engineering as a way to escape the tyranny of heredity and improve man's intellect and other capacities.

Now Sinsheimer believes otherwise. In a talk given this June at the University of California, he warned of the dangers that may accompany new knowledge. " 'Know the truth and the truth will make you free' is a credo carved on the walls and lintels of laboratories and libraries across the land," Sinsheimer observed. But, he added,

> We begin to see that the truth is not enough, that the truth is necessary but not sufficient, that scientific inquiry, the revealer of truth, needs be coupled with wisdom if our object is to advance the human condition. . . .
>
> The twentieth century has seen a cascade of magnificent scientific discoveries. Two, in particular, have extended our powers far beyond prior human scale and experience. In the nucleus of the atom we have penetrated to the core of matter and energy. In the nucleic acids of the cell we have penetrated to the core of life.
>
> When we are armed with such powers I think there are limits to the extent to which we can continue to rely upon the resilience of nature or of social institutions to protect us from our follies and our finite wisdom. Our thrusts of inquiry should not too far exceed our perception of their consequence. There are time constants and momenta in human affairs. We need to recognize that the great forces we now wield might—just might—drive us too swiftly toward some unseen chasm.

Genetic engineering by the recombinant DNA technique is a thrust of inquiry that may be perilous in its consequences, Sinsheimer has come to believe. "I do fear," he said in the same talk, "that there are potentially grievous risks—of the spread of slow viruses or of cancer or of new pathogens, yet unborn, evolved from our inventions."

What has turned Sinsheimer from advocate to skeptic, from enthusiasm about genetic engineering to misgivings so grave as to set him on a different path from the mass of his colleagues? While in Washington for the Senate hearings on recombinant DNA, Sinsheimer explained in an interview some of the reasons for his change of mind.

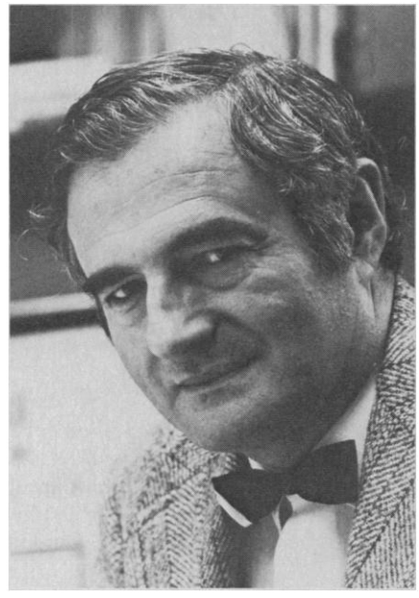
In his earlier view of genetic engineering, he says, "I thought of very careful experiments to replace gene A with gene B—it never occurred to me that anyone would do a shotgun experiment [in which all the genes of an organism are manipulated more or less at random]." He was also more optimistic then that genetic engineering could be controlled.

Asked why more colleagues do not share his view, Sinsheimer replies that "I have been thinking about these things for longer than most of the people who are now more sanguine than I am. Scientists can be very insular, and to some degree they have to be. To be a good scientist takes an awful lot of dedication, and you have to really believe in it and believe that what you are doing is good and beneficial. It is such people who are less likely to entertain other points of view."

A certain narrowness of view is Sinsheimer's chief complaint with the NIH guidelines governing research on recombinant DNA. "This is a technology that was developed by scientists to solve their own problems, and they are still locked into that mode of thinking," he observes.

When he reviewed the guidelines, at the NIH's request, Sinsheimer found that they had dealt reasonably well with the immediate health hazards but "had given no thought to the evolutionary question." As to why the committee set up by the NIH overlooked this question, Sinsheimer remarks that it was "implicit for the guidelines committee to concern itself with health hazards—it simply was not constituted to cope with the larger issues."

By the "evolutionary question" Sinsheimer refers to the fact that some of the genetic manipulations made possible by the new technique may be of a type which evolution has been at pains to prohibit. Many recombinant DNA experiments require the insertion of genes from the cells of higher organisms, or eukaryotes, into prokaryotic cells such as bacteria. Sinsheimer conjectures that the apparent barrier to genetic interchange between eukaryotes and prokaryotes is one that is there for good reason, and that to transgress it by creating prokaryote/eukaryote hybrids in hundreds of laboratories throughout the world is to risk causing unpredictable—and irreversible—damage to the evolutionary process. For example, the barrier might be there to protect the genetic machinery of higher cells from prokaryotic take-over.



Robert L. Sinsheimer

Sinsheimer has not been greatly impressed with the arguments brought forward against his barrier theorem. A common objection, raised for instance by Baltimore at last month's hearings, is that the prokaryote/eukaryote barrier is being broken all the time in nature, as for example when bacteria in the gut take up digested fragments of DNA. "That is an ad hoc argument. It is even worse than ad hoc—it is contrived," says Sinsheimer. Since there is no evidence that prokaryotes and eukaryotes do in fact exchange genetic information, those who say that microorganisms are always taking up eukaryotic DNA have to couple this assumption with the hypothesis that whenever it occurs, the organism dies out.

Another argument is that all the genetic combinations that can occur have already occurred in the course of evolution. Sinsheimer feels intuitively that this is not the case. He observes too that many who make the argument also speak of the benefits of genetic engineering, a proposition which is predicated on the opposite assumption.

To those who contend that any new and harmful organisms accidentally created by the technique would not survive in nature, Sinsheimer replies that one could certainly design some quite fearsome microorganisms by the recombinant DNA technique. Can one be certain that such organisms, if they arose inadvertently, would always be at a disadvantage?

The intentional misuse of the recombinant DNA technique is another of the broader issues which Sinsheimer feels has been neglected in the guidelines approach. The guidelines deal with the immediate health hazards that scientists can foresee, but they don't take account of the hazards to other sectors of society, of the fact, for example, that the technique can be used by other sectors besides scientists, such as the military or terrorist groups.

Sinsheimer considers that deliberate misuse of the technique is a serious possibility.* The problem is analogous to that of nuclear terrorism, he says. "It may well be that there are some technologies that you should not use, not because they can't work but because of the social dangers involved and the repression that would be necessary to prevent social danger."

The nuclear genie is now out of its bottle for good or ill, and the crucial time of grace for instituting control over the recombinant DNA technique is probably already over. Has a unique opportunity been missed? Sinsheimer returns to his theme of the consequences of new knowledge: "We have gone along for several hundred years with the belief that knowledge and the means for acquiring knowledge are always beneficial.

"The situation that first led anybody to question that assumption was the atomic bomb. I think that a lot of people wish there were a way to forget all about nuclear physics but there is not. For a while, many people hoped that that was an anomaly.

"But now here comes another one. How do you cope with this new observation that some kinds of knowledge and some kinds of technology can be very dangerous? We have no assurances that science will not lead us into a very dangerous world.

"How do you control that without interfering with a lot of the freedoms that people [scientists] have cherished? That is something we are only groping toward. . . .

"How do you make policies for an issue which may take 50 years to re-

*He declines to discuss specifics, but some misuses are obvious enough. For example, a biologist might conclude that the surest way to save a large number of human lives would be to prevent lung cancer by improving upon the natural virulence and distribution of the tobacco mosaic virus. A good experimentalist, maybe, could perform this and other, more injurious, operations with today's conventional methods; with the recombinant DNA technique, however, such manipulations may soon be a cookbook matter, accessible to those with lesser skills and direr motives.

solve? Our government, at least in the past, has not been ready to make long-term decisions.

"Some of my colleagues feel that it is the scientist's job to do science, and society's job to cope with what he does. I disagree with this in principle. The scientist must keep the public informed and involved because nobody else will.

"It is entirely possible, as Chargaff said, that the future may curse us [for the consequences of the recombinant DNA technique]. Really only the interests and concerns of the scientific community were involved in formulating the guidelines."

Those who formulated the guidelines have shown a curious reluctance to come out and debate Sinsheimer at his own broad level of argument. The pursuit of knowledge is held even by nonscientists to be a distinguishing value of society†. Is that the answer to Sinsheimer's belief that the right of free inquiry should not be absolute in the case of recombinant DNA? If it is, nobody has rushed forward with it in any of the public documents intended to justify the NIH guidelines.

Sinsheimer believes that one step leads inevitably to another, that the recombinant DNA technique is the beginning of the genetic engineering of bacteria, of plants and domestic animals, and ultimately of man. "Do we want to assume the responsibility for life on this planet . . .? Shall we take into our own hands our own future evolution?" Sinsheimer has asked. If any of his opponents had heard the question, they might perhaps have answered to the effect that since man has now insulated himself from Darwinian pressures, some other means of genetic improvement must be found to assure his continued progress as a species. But Sinsheimer, who seems to have a virtual monopoly of long-range thought about the issue, has also provided an answer to the question. He says, in essence, that we aren't clever enough to know, so shouldn't yet try.

The recombinant DNA technique will clearly bring to birth a technology so potent that even its slightest deviations from the intended path may cause grievous perturbations in society at large. Historians half a century from now will no more blame the architects of the guidelines for failing to cope with every possible contingency than do their contemporaries blame Henry Ford for every highway casualty. Yet they may take a certain interest in the quality of the arguments being relied on for riding roughshod over the reservations articulated by Sinsheimer. Would they be very favorably impressed with what is on the record so far?—NICHOLAS WADE

†For example, "America's distinctive values are, most conspicuously, individual freedom, civil and religious liberty, the pursuit of truth," states former Secretary of Defense James R. Schlesinger in the current issue of *Foreign Policy*.

NSF: New Program Criticized as "Appalling" Subsidy to Activists

The biggest fight over the National Science Foundation budget this year did not involve allegedly "un-American" science curricula or silly-sounding research projects or any of the other headline-making topics that have titillated congressmen in recent years. Rather, it focused on a modest new program known as "Science for Citizens" which seeks to improve public understanding of and involvement in policy issues. That program, in the eyes of both proponents and opponents, has the potential for substantially increasing the technical resources of public interest groups that do battle with the government and industry.

The dispute over this relatively minor part of the NSF budget became the chief obstacle to attaining agreement between the Senate and the House on legislation authorizing NSF programs for fiscal year 1977. Conferees from the two houses wrangled for 3 months over the legislation, finally reaching agreement in the waning days of the congressional session.

One House conferee—Representative Mike McCormack (D–Wash.)—was so opposed to the program that he refused to sign the conference committee report recommending authorization for the NSF budget. McCormack told *Science* he considers it "appalling" that the federal government, through NSF, may end up subsidizing groups that are intervening to block programs that the government has already authorized. "The intervening groups are rubbing their hands and drooling over this," he complained.

The driving force behind the Science for Citizens effort is Senator Edward M. Kennedy (D–Mass.), who has been waging battle on many fronts to increase public participation in technical decision-making and to provide government funding for the impoverished citizen groups that seek to influence public policy. From his seat as chairman of the Senate subcommittee on NSF, Kennedy sought to launch the program last year but was beaten back and had to settle for a planning study by NSF.

That study, which was based in part on testimony gathered at seven public hearings in different regions of the country, was submitted to Congress in February. It set forth nine options for conducting the program but tried to keep NSF out of politically sensitive areas by stating that "no direct financial assistance is envisioned to public interest groups." The report argued that NSF is not an appropriate organization to determine which public interest viewpoints deserve funding. It also claimed that provision of such funding "could potentially place NSF in an advocacy position beyond its mandate and inappropriate to its mission." The Foundation clearly had modest plans for the program. Its budget request sought only $300,000 to continue development of the program and to conduct trial runs of several of the options.

The go-slow approach seemed just fine to the House Committee on Science and Technology, which endorsed both the $300,000 support level and the notion that "NSF should remain as far away as possible from direct assistance to citizens' groups." The House committee urged NSF to "concentrate on provision of educational and informational materials, and not become involved with citizen litigation or direct intervention in administrative proceedings." Its chief concern was that NSF might get embroiled in political disputes that could jeopardize support for its other programs.

But Kennedy and his cohorts in the Senate had more ambitious plans. They recommended funding of $3 million and suggested that some of it go directly to citizen groups to help them acquire "necessary technical expertise." The Senate

(Continued on page 347)