ommends that such studies not be arbitrarily ended at the two-year mark but instead be continued over the "lifetime" of the rodents, defined as the point when only 20 percent of the starting group is alive. For rats, that is more apt to be around 2½ years than 24 months.

There is responsible speculation that some of the major studies conducted on the recently banned Red No. 2 failed to detect evidence of cancer because they lasted only two years. That, at least, is the proposition put forth by David W. Gaylor, principal biological statistician at the FDA's National Center for Toxicological Research in Arkansas, who performed the statistical analysis that was most instrumental in knocking Red No. 2 off the market. Gaylor concluded that high doses of Red No. 2 administered in a recent FDA study resulted in a statistically significant increase in the incidence of cancer among aged female rats, with most of the cancers being detected after 24 months. Similarly, a Russian study which concluded that Red No. 2 is a carcinogen lasted 33 months. In contrast, a massive feeding study of 800 rats at the FDA in the 1950's, which found that Red No. 2 posed no hazard, lasted only 24 months. That led Gaylor to suggest in a 31 December memorandum that "possibly, the reason cancer was not detected" in the 1950's rat studies "was that those experiments were terminated at 24 months."

Anderson, of Allied Chemical, says that the Canadians also declined to approve Red No. 40 until a life-time feeding study in mice is completed. Our own FDA now generally recommends life-time studies in two rodent species, but back in 1971 it approved Red No. 40 based on such studies in only one rodent species, the rat.

In an effort to meet the Canadian requirements, Allied is sponsoring new long-term tests at Hazleton Laboratories in both rats and mice, with the dye being administered initially to the parents and then through the life-times (or close to it) of the offspring. The parental generation had not received the dye in the original tests.

Anderson stresses that no one has claimed any of the test data generated so far indicate that Red No. 40 is a hazard. The only question is whether the tests are adequate to demonstrate the dye's safety. He also notes that the standards used in toxicity testing are under constant revision as the science develops. The data submitted by Allied were considered adequate evidence of safety by the standards of 1971, he said, and Allied has since subjected the dye to additional testing to keep toxicity information current.

Anderson estimates that Allied has spent more than $500,000 testing Red No. 40, including studies of acute and subacute toxicity in rats and dogs, a two-generation feeding study in rats to measure effects on reproduction, skin tests in rabbits, mice and humans, metabolic studies in dogs and rats, and a teratology study in rabbits. None of the tests, says Anderson, have suggested a hazard.

Allied launched the research that led to development of Red No. 40 in the mid-1960's because one red dye had been removed from the market in 1961 and another was restricted in 1965. The company screened some 90 synthetic chemical compositions, picked out a handful for further testing, and finally settled on Red No. 40 (trade name: Allura Red AC) as the best of the lot. The bulk of the safety testing was performed at Hazleton between 1965 and 1970. Upon its completion, Allied petitioned the FDA to approve the color, and the FDA granted a "permanent" approval in 1971. In that same year, Allied submitted a petition to the Canadians, only to have it turned back three years later after prolonged review and negotiations.

Allied has a patent on Red No. 40 but is said to have licensed at least two other manufacturers—H. Kohnstamm & Co., Inc., and Warner-Jenkinson Manufacturing Co.—to produce the dye. If Red No. 2 finally disappears from the market (it has been banned by the FDA but the manufacturers have appealed the decision to the courts), Red No. 40 is expected to attain widespread usage in foods, drugs, and cosmetics. Unless, of course, the searchlight is now turned on Red No. 40 and flaws are found in *its* safety pedigree as well.

—PHILIP M. BOFFEY

Recombinant DNA: Guidelines Debated at Public Hearing

After the first atomic devices were successfully developed, Robert Oppenheimer made the perhaps sententious remark that physicists had now known sin. That biologists may at least be moving out of an age of innocence was a point made at a hearing held on 9 and 10 February on the new method of genetic manipulation afforded by the recombinant DNA technique. "The research we are talking about," observed Robert Sinsheimer of the California Institute of Technology, "marks a transition from a primarily analytic base to a much more synthetic base, and I don't know if the implications of that have sunk in for any of us."

The hearing was convened by Donald S. Fredrickson, director of the National Institutes of Health, to review the draft guidelines for use of the technique that were drawn up last year by an NIH committee (*Science*, 19 December 1975). The technique has been under a virtual embargo since July 1974, when a National Academy of Sciences committee under Paul Berg of Stanford University called for a worldwide moratorium on certain of the experiments the technique makes possible.

Last week's hearing pitched both defenders and critics of the present draft guidelines in debate before a special advisory committee to the NIH director. The 20-member group included David L. Bazelon, chief judge of the District of Columbia Court of Appeals, Peter B. Hutt, former general counsel of the Food and Drug Administration, and Philip Handler, president of the National Academy of Sciences.

The prime significance of the hearing was probably that it created the first opportunity for people other than scientists to comment on the rationales and procedures developed within the scientific community for handling the new technique. The reaction was predominantly favorable. Hutt, for example, who had mastered the salient issues as quickly as anyone on the director's committee, remarked that the scientific community merited "enormous praise" for bringing the matter to the fore and that "if Berg and his colleagues don't deserve the Nobel prize for medicine, they deserve it for peace."

At the same time Hutt and other members of the committee clearly attached considerable weight to the positions taken by critics such as Richard Goldstein of the Harvard Medical School, and Allen Silverstone of the Massachusetts Institute of Technology, who spoke for groups that be-

lieve the proposed guidelines are still too lax.

No votes were taken at the hearing. Instead, NIH director Fredrickson announced he would make his decision on the basis of the hearing record and committee members' written opinions, and would have any modifications prepared by 1 April for consideration by the NIH committee which drafted the guidelines. During the hearing Fredrickson was showered with widely divergent advice on issues ranging from laboratory safety procedures to such imponderables as whether the technique constitutes an interference with evolution and whether a society can afford to halt research because of fear of the unknown. His decision on these points should be interesting, particularly if he follows Judge Bazelon's advice to lay out with great specificity the reasons for every step he does and doesn't take. For the fact of the matter, Bazelon told him, is that the public is entitled to know.

It is not so surprising that biologists would one day arrive on the threshold of being able to understand the genetic program of living organisms and to create new such programs. What does seem to have surprised even those working in the field is that the day has arrived so soon. "Understanding how the genes of higher organisms are expressed and regulated, which was a pious dream a few years ago, is now within our grasp," Berg observed at the outset of the hearing.

What has made the dream possible is the discovery of a class of enzymes used by bacteria to recognize and destroy foreign DNA. Known as restriction enzymes, they serve as a marvelously apt scissors-and-paste kit at the gene level. They cut DNA molecules at particular sequences that occur on average a few genes apart, and they do so leaving "sticky ends" which allow a genetic segment from one organism to be joined to a similarly cut segment from another, the hybrid molecule being known as a recombinant DNA.

But the means to this answer to the genetic engineer's dream is also an aspect of the problem. Restriction enzymes exist to restrict the exchange of genetic information between species. To create new organisms by joining genes from different species is to transgress barriers which, possibly for good reason, may not have been crossed before in evolution. A more specific danger is that many proposed uses of the new technique will involve inserting animal genes into the human gut bacterium *Escherichia coli*, which is the organism of choice because so much is already known about it. The new genes could confer malign properties on the bacterium, which, at worst, might escape and cause an epidemic. Such a hazard is made less remote by the fact the so-called shotgun experiment, in which the total DNA of an organism is cut into fragments and inserted into *E. coli*, involves endowing the bacteria with at least some genes of definite potential hazard. Even a gene specifying a hormone or enzyme could be hazardous to man if it were expressed in *E. coli*.

Much of the debate at last week's hearing was disjointed and uneven, probably reaching its least sophisticated point when Berg produced a string of colored beads to explain recombination. The cut and thrust of argument took place between those with a long involvement in the guideline drafting process, who generally believe that the present guidelines are strict enough, if not too strict, and members of the two Boston-based groups who consider that a more cautious approach is justified. The Boston groups, unlike many of their opponents, have no personal interest in recombinant DNA experiments, a debating advantage to which they added by presenting their case in a moderately stated way.

The essence of the critics' position is that the guidelines, though admirable in intention, do not go far enough. The guidelines propose four levels of physical containment for recombinant DNA experiments, designated P1 to P4 in increasing order of severity. Goldstein, speaking for the Boston Area Recombinant DNA Group of Science for the People, criticized the guidelines' position on shotgun experibiological practice and that P3 is the first meaningful level of containment, though even that is questionable. The argument evidently made an impression on the committee; Handler, for example, said he shared the concern about physical containment, adding that "I don't know that P1 and P2 contain anything."

Goldstein also criticized the use of *E. coli* as host for recombinant DNA molecules, because it infects man. Yet abandonment of *E. coli* until another host organism is developed would impose an indefinite moratorium on many promising aspects of the technique. Berg defended the bacterium's suitability by stressing that no other organism can be so easily manipulated.

Both Goldstein and Silverstone, who represented the Genetics and Social Policy Group of Science for the People, criticized the guidelines' position on shotgun experiments as inconsistent. The guidelines would permit shotguns with the genomes of lower organisms to take place in less stringent conditions than those with higher genomes. According to Silverstone, a shotgun experiment "is just that—a shot in the dark," and all types of shotgun should be treated with the utmost caution.

A vigorous argument that the guidelines are already too strict was presented by Donald D. Brown of the Carnegie Institution of Washington. "When scientists brought up this issue they got some points, but when they tried to control it, that is where all the trouble began," Brown told the hearing. To convince people that they were not self-serving, scientists had boxed themselves into producing super conservative guidelines. The supposed hazards had never been discussed in detail and in his view were remote.

A similar point was made by David Hogness of Stanford University. At each stage in the development of the guidelines there had been an escalation in the recommended safety levels, despite the lack of hard evidence that the imagined risks were any more real than before. "Fear of the unknown has been overemphasized, with the result that there has been an overshoot," Hogness said.

David Baltimore of MIT, a member of the committee that originally invoked the moratorium, told the hearing that the guidelines' position on work with tumor viruses is so restrictive that "it is only barely possible to go forward."

Baltimore derided the idea that the joining of genes from different species might be adding something to nature that wasn't there before. "The shuffling and mixing of DNA molecules has gone on for eons, and if it were dangerous to add DNA to a plasmid [a kind of bacterial chromosome used as the vehicle for the recombinant], I think we would know it already." Sinsheimer objected that that was like saying the human species had evolved in the presence of background radiation so therefore radiation was harmless. Sinsheimer, who is concerned that the technique risks compromising natural species barriers, particularly those between bacterial-type and higher cells, conceded that random recombinations of DNA have probably occurred in evolution but "we don't know at what rate." He warned the hearing that "what we are doing is almost certainly irreversible. Knowing human frailty, these structures will escape, and there is no way to recapture them. The hazard, if there is a hazard, will not be like DDT or PCB's or aerosols, which you can just stop manufacturing."

Burden of Proof

Under the weight of such intangibles the discussion often became little more than a plea to intuition. "Seriously, what is the rush to do these experiments?" asked John Sedat of Yale. Yet according to Baltimore, the world has waited long enough for the guidelines and they should be issued as soon as possible. Proponents of going ahead perhaps had a more complex case to

argue, particularly in the face of a suggestion by Hutt that they carried the burden of proof to show that no hazard existed. Rigorous adoption of such a principle would make much research hard to justify. Hutt seemed later to modify this position when he said that, since scientists had taken the initiative in raising the safety issues, they should be allowed to keep it.

But he warned that they might lose the initiative if they failed to take certain additional steps. One omission was public participation. "I do not believe that the public's rights should be affected by guidelines drawn up by any group which has not undergone the procedures for public participation laid down in the administrative procedure act," Hutt said.

Another loophole in the guidelines is that they do not address the question of proliferation. Although analysis of a recombinant DNA experiment requires expensive equipment, the simple construction of the molecules probably is or will be within the capability of a high school laboratory. But the guidelines are at present enforceable only by denial of NIH funds, and would not apply to industry, foundations, schools, and other laboratories. Congress, in Hutt's view, is unlikely to let such an anomaly exist. It could be abolished, he suggested, by exercise of an obscure law in the Public Health Service Act which gives the Surgeon General sweeping powers to control communicable diseases.

The hearing has left Fredrickson with a decision that is both technical and political in nature. Because almost all research with the technique has been embargoed, not much new has emerged to add to the technical arguments. There is still no clear answer to such elementary questions as whether bacteria such as *E. coli* can synthesize the protein products specified by the genes of higher organisms. If they cannot, the risk of inserting such genes into bacteria is obviously much reduced. In political terms, the hearing seemed to underline how hard it is for those with a direct interest in the experiments to make a fair case for themselves. Several speakers, for example, criticized the guidelines for allowing shotgun experiments with insects, referring indirectly to an experiment now under way in Hogness' laboratory. Possibly too little attention was paid to a technique developed by Hogness and a colleague which removes much of the objectionable random element in a shotgun experiment.

A chief lesson of the hearing was thus that the rationales behind the guidelines, the reasons for pressing ahead with the experiments in face of an irreducible minimum of risk, need to be spelled out in terms that are persuasive to Congress and the public. Up to now, that argument has only been made to other scientists, who have an intellectual interest in the results. Fredrickson's second problem, if he considers it within his ambit, will be to suggest ways for controlling the technique on a national basis. Here again, discussion hitherto has focused on practice in the best laboratories. The real problem is how to maintain control over the technique when it gets into the hands of the worst.

—NICHOLAS WADE

Pest Control: NAS Panel Warns of Possible Technological Breakdown

The U.S. government will, over the next decade, be looking increasingly to the high productivity and abundance of American agriculture as a major source of national economic and political strength in a world in which food may be in desperately short supply. Yet a National Academy of Sciences (NAS) study committee is now warning that future agricultural productivity is threatened by a possible breakdown in chemical control of pests.

In a five-volume report released 5 February, the NAS committee,* which was chaired by Donald Kennedy, a professor of biology at Stanford University, pointed to three developments that are "challenging" the effectiveness of chemical technology.

- Genetic resistance has appeared in many "target" insect pests. Since the discovery 25 years ago of resistance to DDT in the housefly, some 200 other insect species have been found to exhibit genetic resistance to chemical pesticides. In fact, "most of the major pests" affecting agriculture and public health have been found resistant to some chemicals, at least over part of their geographic range.
- "Natural" pest control mechanisms are often disrupted, as when beneficial insects as well as target pests are killed by a chemical compound toxic to a broad spectrum of insect life. In California's San Joaquin Valley, for example, the organophosphate insecticide used by cotton growers to prevent outbreaks of *Lygus*, a plant-sucking bug prevalent throughout the growing season, also kills certain predators which normally control the bollworm, a late-season pest. Moreover, predacious insects seem not to develop genetic resistance to chemical insecticides as readily as do target pests.
- Use and development of chemical pesticides is increasingly constrained by laws and regulations adopted in the interest of environmental protection and occupational health and safety. Several important chlorinated hydrocarbon pesticides, including DDT and aldrin and dieldrin, have been banned already, as have certain mercurial fungicides. Still other commonly employed chemicals, including arsenicals, certain phenoxy herbicides, and the rest of the chlorinated hydrocarbon pesticides, could in time be either banned or severely restricted in their use. Furthermore, development of new pesticides is made more difficult and expensive by the new regulatory regime. Although not decrying the new laws and regulations, the report says that they must be taken into account, and perhaps modified in certain particulars, in the shaping of alternative pest control strategies.

According to the report, successful alternative strategies will require further use and development of such approaches and technologies as the following:

1) Breeding pest-resistant plants and introducing genetically modified pests, such as sterile males, into natural populations.

2) Developing bacterial and viral agents to which farm pests will be vulnerable—a control technology already showing "great promise." †

3) Developing "third-generation" chem-

* Others besides Kennedy on the Executive Committee responsible for the study were Perry L. Adkisson, entomologist, Texas A & M University; Samuel R. Aldrich, Agricultural Experiment Station, University of Illinois, Urbana; Donald L. Dahlsten, entomologist, University of California, Berkeley; John E. Davies, epidemiologist, University of Miami School of Medicine; Boysie E. Day, plant physiologist, University of California, Berkeley; Carl Gotsch, Harvard University; James E. Krier, professor of law, University of California, Los Angeles; Michael C. Latham, nutritionist, Cornell University; Matthew S. Meselson, biochemist, Harvard University; William W. Murdoch, biologist, University of California, Santa Barbara; Kusum Nair, visiting researcher at East-West Food Institute, Hawaii; Charles E. Palm, professor of agricultural sciences, Cornell University; Vernon W. Ruttan, Agricultural Development Council, New York; and Roy A. Young, vice president for research and graduate studies, Oregon State University.