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August 1, 1977

Mr. Norman J. Latker
Chief Patent Branch
Office of the General Counsel
Westwood Building
Room 5A03
Bethesda, MD 20014

Dear Norm:

I appreciate your keeping us up to date on the recent political developments in the recombinant DNA area, particularly the summary that came in today from the Sunday, July 24 Washington Star.

From this distance it is hard to keep abreast on what is happening and to know just when our efforts would be best expended on which author's bill. It seems that the best agency to monitor recombinant DNA activities would be DHEW rather than Kennedy's "National Recombinant DNA Safety Regulation Commission." (Even the title is a tip off of things to come under the Kennedy bill. Further, the word "regulation" is redundant - you don't regulate safety - you regulate hazards.) We would much prefer the whole matter in an agency that is science-oriented such as DHEW. There the proprietary aspects of our programs would, we think, be accorded the proper treatment.

This fall things will probably heat up again on this matter. I hope you or Ray Woodrow will keep us advised so that we can do our lobbying bit where it is needed.

With best regards,

Sincerely,

G. Willard Fornell
Patent Administrator

GWF:djl
cc: Ray Woodrow ✓



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Ray Woodrow
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- Norman Lelker
HEW

Drug firms becoming active in DNA research

Pharmaceutical companies see opportunities in DNA recombinant work, and think they can meet federal laws better than other labs

It is sometimes forgotten in the furor of the debate about the subject that recombinant DNA techniques are not only very useful for fundamental research in molecular biology, but have several commercial applications of potentially great importance. It is not only academic and government laboratories that are interested in transplanting pieces of DNA carrying specific genetic traits into cells where they would not ordinarily be found, but industrial laboratories as well. Some companies already are conducting recombinant DNA research in the U.S., a few are getting ready to enter the field, and several others have an interest, if not an active research program, in the area.

Probably fewer than a dozen companies actually are supporting research involving recombinant DNA or have definite plans to begin this type of research at present. Most of these are drug companies interested in developing new and cheaper antibiotics and other biologically synthesized medicines. A few companies are interested in the technique for its application to agriculture (especially the development of nitrogen-fixing plants) or for developing microorganisms to dispose of pollutants and make methane and other fuels. And a few companies are supporting limited research in recombinant DNA as a part of their basic research programs with no specific application in mind as yet.

Unlike their academic and governmental counterparts, industrial researchers working with recombinant DNA seem to be united in their opinion of the risk involved in these experiments. They applaud the safety aspects of the guidelines developed by the National Institutes of Health last year that govern such research. But they also express no doubt in their ability to conduct recombinant experiments safely and with no unusual risk to their own employees, people in nearby communities, or the environment.

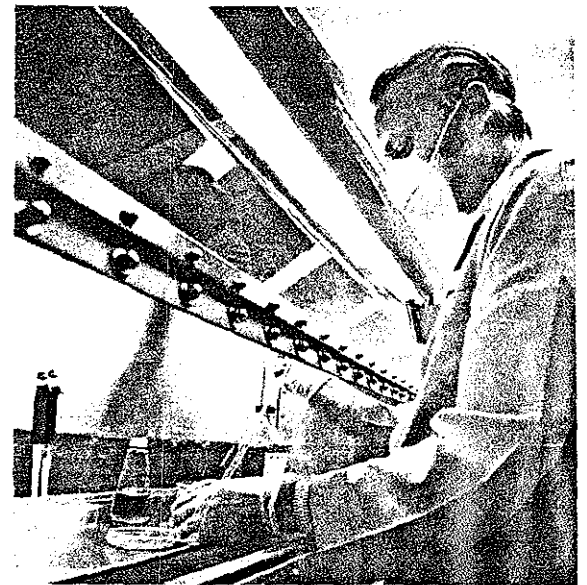
At the moment, the NIH guidelines are only strictly applicable to researchers who receive their funding from NIH or from other government agencies that have adopted the guidelines—a category that does not include any of the industrial re-

search that is being done. However, all of the companies contacted by C&EN say they are in voluntary compliance with the NIH guidelines for their recombinant DNA work. Legislation currently is being worked out in Congress and in many state and local areas that would regulate industrial as well as academic and government-supported recombinant DNA experiments.

Fairly typical of the sort of industrial research going on is that at Upjohn. The company has been involved in recombinant DNA research for about a year, acquiring techniques and developing expertise, according to Dr. Joseph E. Grady, research head for infectious diseases. For Upjohn, the goal of such research is the development of new or cheaper antibiotics. So far the experiments all have been at the EK1, P1 level—the level considered the least dangerous by NIH and requiring the least amount of special containment precautions. With more practice, Upjohn will be moving into experiments with antibiotic-resistant microorganisms requiring more rigorous P2 containment. Like most research-oriented drug companies, Upjohn has been doing more conventional genetics experiments with infectious organisms and drug-resistant bacteria for many years and already has research facilities that more than meet the NIH requirements for P2 research. The company hopes to construct a still-higher-level P3 facility next year.

So far, the Upjohn work has all been done in the bacterium *Escherichia coli*, and, says Grady, Upjohn researchers will be working with this organism for the foreseeable future. Eventually, and it hopes before its competitors, the company hopes to do experiments with mammalian DNA and in microorganisms other than *E. coli*—particularly the *Streptomyces*, which are the most important producers of antibiotic medicines. Such experiments are not possible today under the NIH guidelines. They require the highest-level (P4) containment facilities, which do not exist, and certification of the safety against infestation of the microorganisms that would be used, which cannot be done without much more development work. On the other hand, Upjohn is not yet ready to do the experiments.

The guidelines, Grady explains, are shaping the direction of the work at Upjohn, particularly by requiring the use of *E. coli*, but they are not inhibiting research. He is confident that as Upjohn gains experience with the techniques, it will be able to convince NIH or some other federal regulator of the safety of its work and be able to continue it.



Biological containment cabinet prevents escape of organisms in DNA studies

Abbott Laboratories has not started recombinant DNA research yet, but it is getting ready to begin later this month. It will begin at the P2 level and go on to P3 experiments in the fall, according to Dr. Ronald G. Wiegand, director of antibiotics and natural products research. Like Upjohn, this research will aim at developing antibiotics and medically important proteins like blood coagulants.

"I'd much rather work with recombinant DNA than with a known infectious agent," Wiegand says, summing up the attitude of most drug company researchers. For recombinant DNA experiments, "the risks are hypothetical. In some of our other work we are dealing with known infectious agents. With recombinant DNA we have added biological containment to ensure safety, which is really a whole other level of safety. So we have more safety with less risk. To my mind that adds up to less danger."

Like Upjohn, Abbott's original experiments will be with *E. coli*, including some with the specially crippled strain developed by Dr. Roy Curtiss III of the University of Alabama and certified by NIH for more hazardous EK2 level experiments. Using this microorganism poses no particular problems for Abbott, Wiegand says, since it already has been developed and is available to the company from Curtiss. Eventually, commercially useful experiments probably will need to be done in another microorganism and in quantities greater than the 10-liter restriction NIH has set on recombinant experiments for now, Wiegand agrees. But he is quite



Other views changing on hazards of DNA research

Academic scientists, too, appear to be growing more confident of their ability to conduct recombinant DNA experiments safely. At last month's Gordon Research Conference on Nucleic Acids, held in New Hampshire, scientists actively working in the field of nucleic acid research drafted an open letter to Congress expressing concern that unnecessarily restrictive legislation might deny society the benefits of recombinant DNA research. The letter, signed by 137 of the 160 scientists attending the conference, also will be published in *Science*. The letter is particularly significant since it was an open letter to *Science* from the researchers at the same Gordon Conference in 1973 that led to the initial moratorium on recombinant DNA experiments and eventually to the NIH guidelines.

The letter says, in part:

"We, members of the 1977 Gordon Research Conference on Nucleic Acids, are now concerned that legislative measures now under consideration by Congressional, state, and local authorities will set up additional regulatory machinery so unwieldy and unpredictable as to inhibit severely the further development of this field of research. We feel that much of the stimulus for this legislative activity derives from exaggerations of the hypothetical hazards of recombinant DNA research that go far beyond reasonable assessment.

"This meeting made apparent the dramatic emergence of new fundamental knowledge as a result of application of recombinant DNA methods. On the other hand, the experience of the last four years has not given any indication of actual hazard. Under these circumstances, an unprecedented in-

roduction of prior restraints on scientific inquiry seems unwarranted."

NIH's Recombinant DNA Molecule Program Advisory Committee, the group that drafted the present NIH guidelines, is taking a similar position. In its meeting on June 23, it proposed a number of changes to the guidelines which it will be submitting shortly to NIH director Donald S. Fredrickson. In a preface to the revisions, the committee explains its proposals as follows:

"The present revisions take into account many communications both from scientists and nonscientists since the original publication of the guidelines. During this period the committee has also become better informed about the general ecology and epidemiology of infectious microorganisms. Of particular relevance has been the information received from many medical microbiologists including data from experiments with *Escherichia coli* K-12. These experiments include a demonstration that strain K-12 cannot be made pathogenic even when provided by standard genetic techniques with the genes from known toxins or other pathogenic properties. Other relevant experiments that have been reported show that the incorporation of foreign DNA does not increase, but rather tends to decrease, the general fitness of microorganisms and this further contributes to the unlikelihood that cells carrying recombinant DNA will survive in nature. Indeed, everything we have learned tends to diminish our estimate of the risk associated with recombinant DNA in *E. coli* K-12. Nevertheless, the revised guidelines continue to be deliberately restrictive with the intent of erring on the side of caution."

optimistic that the developing regulations will allow these transitions when the scientific expertise to support them has been developed. "We will have some obligation to show that these things are safe before we do them," he explains, "but that is what we would do anyway."

One advantage that companies like Abbott will have over universities and other private laboratories in doing recombinant DNA research is their experience with complying with federal research guidelines. The drug industry already is regulated extensively by the Food & Drug Administration and other federal agencies, Wiegand points out, and has developed procedures for assuring compliance with external regulations. Academic laboratories, for the most part, do not have this experience. "It's not difficult to meet the NIH guidelines," he says. "It's assuring that you meet them that takes the most time because you have to have written records and that's what takes the time and the money." Companies like Abbott that have full-time biohazards officers and extensive medical monitoring

of employees will not have much difficulty in meeting the NIH safety requirements, he feels.

General Electric's research laboratories have been conducting limited experiments using recombinant DNA techniques for about two years, explains Dr. Ronald E. Brooks, who manages the physical chemistry laboratory in the company's environmental unit. The project grew out of GE's interest in microorganisms to clean up oil spills, but the work itself is characterized as basic research with no particular application in view. It is a very small-scale effort involving only three professionals and aims at developing a bacterial host that would be safer than *E. coli*. The work, which concentrates on the bacterium *Pseudomonas putida*, is similar to work that NIH is sponsoring at various universities to develop alternative host systems. Like this university work, Brooks says, the research being done at GE is being reported fully both in the open literature and directly to NIH.

"There's no question in my mind that

our work is several orders of magnitude safer" than that being done at universities, Brooks says. Full-time safety reviewers, state and federal inspections, a more extensive employee medical program, and the requirements placed on the company by its insurance carriers all add to the safety of the research.

Another company that has been working with recombinant DNA for several years is Eli Lilly. The work grew out of the company's viral oncology research program, explains Dr. Irving S. Johnson, research vice president. When restriction enzymes became available they were incorporated into these projects, thus making them recombinant DNA projects. Potential applications at Lilly include the synthesis of important proteins, including insulin. The work is primarily at the P1 and P2 levels, Johnson says, although Lilly does have one P3 research facility.

Lilly's experience has been that putting genes into an environment that is foreign to them, as is done in recombinant experiments, lessens the viability of the organism and lowers the risk involved in working with the organism, Johnson says. For a company that is used to working with infectious agents and disease-resistant bacteria in relative safety, recombinant DNA experiments are not viewed as posing a serious threat, he says.

Johnson is concerned, as are those from other companies, with the effects of early disclosure of research directions on the company's competitive position. Some of the proposed federal legislation would set up biohazards review committees composed in part of people not connected with the company being monitored. Revealing research proposals to such a committee might jeopardize eventual patent rights, the companies believe. They would prefer a biohazards committee composed entirely of company employees, although some of them could come from entirely unrelated areas within the company, such as personnel. Such committees already exist at Lilly and many other companies, Johnson points out. Alternatively, companies believe that review and approval of research plans by NIH or some other federal agency that could maintain the confidentiality of research goals also would provide both safety and security.

Rebecca L. Rawls, C&EN Washington

Birthday conference for Levich stirs protests

For three days last week, more than 100 scientists from 13 countries gathered at Oxford University in the U.K. for a conference on "Physical Chemistry and Hydrodynamics" honoring the 60th birthday of a pioneer in this interdisciplinary area, calling him one of the "most prolific and original members" of the world scientific community. In some 80 papers, they discussed developments, and strongly expressed their esteem for their colleague, "both as a scientist and as a man."