Gene Transplant in Mammalian Cells

Stanford University scientists last week announced the first successful transplant of a functioning gene from one mammalian species to another using recombinant DNA techniques.

The achievement, inadvertently revealed by Stanford biochemist Paul Berg at a press conference during last week's convention of the American College of Surgeons, is the latest permutation of gene transplant techniques. In earlier work, bacteria were coerced into expressing a higher organism's genes when yeast genes, transported into *Escherichia coli,* directed protein manufacture (SN: 3/12/77, p. 163). Genes of successively higher organisms and for more complex proteins have been transferred to and made to function in bacteria: rat insulin genes (SN: 6/17/78, p. 388), genes for human brain hormone (SN: 11/12/77, p. 311) and, finally, genes for human insulin (SN: 9/16/78, p. 195). Berg's work, however — producing rabbit beta chain hemoglobin by infecting African green monkey cells with SV40 virus carrying the hemoglobin gene — is the first successful application of such techniques to mammalian cells.

Visions of vats of bacteria churning out human insulin and other hormones have spurred on researchers in gene splicing experiments with bacteria. The success obtained by Berg and colleagues Richard Mulligan and Bruce Howard is the first glimmer of a different and still distant vision, that of "gene therapy" — replacing defective genes with their normal counterparts. But it is only a small step on a long road, according to other scientists: "We can't even dream of that [gene therapy] yet," said one researcher, who asked not to be named. The value of the Stanford team's work, he and other researchers told SCIENCE NEWS, is not so much the expression of a mammalian gene in a different mammalian species (though this had not been done before with these techniques), but the "technically interesting" achievement of manipulating the rabbit gene into the proper reading frame for transcription from the viral DNA. That achievement, according to Walter Gilbert of Harvard University (a member of the group who induced bacteria to produce rat insulin), seems most immediately useful as a tool in gene mapping and studies of intervening genetic sequences.

Unfortunately, details of the experimental strategy were not released. Berg briefly mentioned the success during a press conference preceding a talk on the general subject of genetic manipulation. When pressed by reporters he refused to give details of the procedure, but later made the announcement public by releasing a statement, again without elaboration, through the university public relations office. Berg declined to answer questions from SCIENCE NEWS and other publications on his techniques, but several workers in the field speculated about the methods the Stanford team used.

According to these researchers, the gene for the beta chain of rabbit hemoglobin was first made about four years ago. It was copied from a template of beta chain messenger RNA, rather than pieced together from a soup of nucleotides as in earlier work. It is likely that this ready availability and the distinctiveness of its product from monkey hemoglobin made it the gene of choice. The SV40 virus was picked as a carrier, one scientist said, because of its specificity to monkey cells and because its DNA sequence is known. Using altered viral DNA as a carrier differs from some other recombinant DNA work, such as the production of human insulin, in which bacteria plasmids, rather than viruses, were rigged with the foreign gene and introduced into *E. coli.*

A researcher who heard a description of some of the work at an earlier conference said Berg used restriction enzymes to cut out a section of the viral DNA that codes for one of the proteins in the viral capsule and inserted the rabbit gene at that point. This step was crucial, he said, because it produced the "minimum perturbation" of the virus while still rendering it unable to reproduce and therefore unable to kill the monkey cells or infect humans. Selecting the correct restriction enzymes and the exact spot for inserting the rabbit gene are the keys to Berg's success, said the researchers. The rabbit gene had to be inserted so that the entire sequence would be oriented and read properly. In itself, such a step is "no big deal" one scientist told SCIENCE NEWS, but valuable because it reveals more detail about gene mapping and expression in this system.

Thus altered, the virus was allowed to infect a culture of African green monkey cells, according to Berg's statement. Though the virus itself could not replicate, it could still instruct the host monkey cells to manufacture the proteins coded for on its DNA, including the foreign rabbit hemoglobin. Unlike bacterial recombinant work, where a foreign protein is produced and excreted into the medium to be collected for use, the rabbit hemoglobin was produced in the monkey cell, potentially a ready supply of hemoglobin for the cell's own use. Researchers said the rabbit hemoglobin was produced as a distinct protein rather than tagged onto a natural viral protein.

According to Berg, a paper on the work will be submitted to NATURE; its publication may clarify many points. □

Nuclear-waste disposal: Feasible . . . later

For years the rhetoric has been the same: Although the government lacks an ultimate strategy for permanent disposal of high-level nuclear wastes, when the time comes that one is necessary — probably in about 10 years — a solution will be ready. The latest report on the subject, prepared by a 14-member interagency review group, comes up with essentially the same conclusion, only the ultimate solution is intimated to be more like 17 years away rather than 10.

In the April 20, 1977, unveiling of his energy plan, President Carter pledged to develop a national nuclear-waste-management policy and program. In March of this year he assembled the interagency review group, representing 14 federal agencies, to put that strategy together. Its draft report, issued last week, contains recommendations based on input from a variety of sources, such as state and local governments, Indian nations, industry, public interest and environmental organizations and the scientific and technical community.

Briefly, the report calls for stepping up the timetable for researching a variety of disposal options, such as placing wastes in salt domes, in bedrock or beneath the ocean floor. Near-term activities should include the building of interim mined-storage vaults where "some tens" of cannisters containing wastes can be studied and, if necessary, retrieved. Intermediate-scale facilities would study the siting of hundreds to 1,000 spent-fuel cannisters in different geological media; the earliest such a facility could be ready is 1986, the report says. To date, most studies have concentrated on burial of wastes in salt. If the initial high-level-waste disposal facility is built in a salt repository, it might be operable by 1988 or 1992, but if the program waits to make the site selection from a broader range of geological options, initial operation would be much closer to 1992 or 1995, the report says.

The problem of what to do with nuclear wastes is a monumental and growing one. In West Germany and the United States, environmental protestors have harangued their governments over the issue of safe disposal. But the problem has escalated in Sweden to the point that two reigning political parties in succession have been