

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 canisters containing wastes can be studied and, if necessary, retrieved. Intermediate-scale facilities would study the siting of hundreds to 1,000 spent-fuel canisters 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

knocked from power over the issue of nuclear plants and their attendant wastes. In 1976 the Social Democratic Party was voted out of office, primarily because of its pronuclear stance. The Center Party, which assumed power, had campaigned on the promise that it would kill nuclear power. In June of last year it passed a Nuclear Power Stipulation Bill, which basically said that unless a nuclear-power-plant operator has a contract stating how and where radioactive wastes will ultimately and permanently be stored, the plant cannot be licensed to operate.

Peter Steen, an energy specialist in Sweden's prestigious Secretariat for Future Studies, said at the time that the law would probably have little effect because Sweden has so few energy options (it lacks fossil fuels, relying on imported oil for 70 percent of its energy). The final toll was reckoned a few weeks ago when Center Party Prime Minister Thorbjorn Falldin resigned over conflicts about what to do with nuclear power. □

Doctors' strike lowered death rate

While the American College of Surgeons was meeting last week in San Francisco, a University of California at Los Angeles researcher was telling an American Public Health Association conference in Los Angeles that a strike by doctors in 1976 significantly lowered the death rate in Los Angeles. Milton I. Roemer said the cause of the decrease was clearly a drop in the number of unnecessary operations performed during that time.

Roemer and his colleague Jerome L. Schwartz compared the death rate in Los Angeles during the five weeks of the strike to that of the same period of time in preceding years. During the five weeks in question, the weekly death rate averaged 19.8 deaths per 100,000 population from 1971 to 1975, but suddenly fell to 16.2 during the strike. After the strike, the rate jumped back to an average of 20.4 deaths per week over the next five weeks.

As a check of their assumption that the decrease was due to a decline of elective surgery, the two public health researchers also examined infant mortality for the same periods, since few young children experience elective surgery. They found no significant change in the number of infant deaths.

When the president of the Los Angeles County Medical Association, Richard F. Corlin, was asked to comment on the report, he replied that although there had been a clear drop in mortality, it would be unfair to "lay it all on elective surgery." Some necessary surgery had also been postponed during the relatively short strike, he said, which merely postponed a risk already facing the patients concerned. □

The sobering cost of alcoholism

Drug statistics are similar in one respect to those of war, natural disasters and others involving death and injury: The reality of human lives lost and of suffering is buried somewhere in the massive figures. Nevertheless, the very proportions of numbers in the latest Health, Education and Welfare department report on alcoholism in the United States are noteworthy:

- An estimated 10 million adults are either alcoholics or problem drinkers.
- As many as 205,000 deaths a year are alcohol-related.
- More than 3 million—19 percent—of the 14- to 17-year-olds in the United States are considered problem drinkers.

Despite this picture, the statistics do indicate somewhat of a leveling off of alcohol consumption and certain accompanying problems. Per capita consumption remains at more than two-and-one-half gallons of absolute ethanol per person (14 years and older), but has not changed appreciably since 1970. Following a sharp increase in cirrhosis deaths during the 1960s, the death rate from liver cirrhosis actually dropped by 6.3 percent in 1975 (the latest year from which data for the study were taken). Still, cirrhosis ranks as the sixth most common cause of death in the United States, with up to 95 percent of the cases estimated to be alcohol-related.

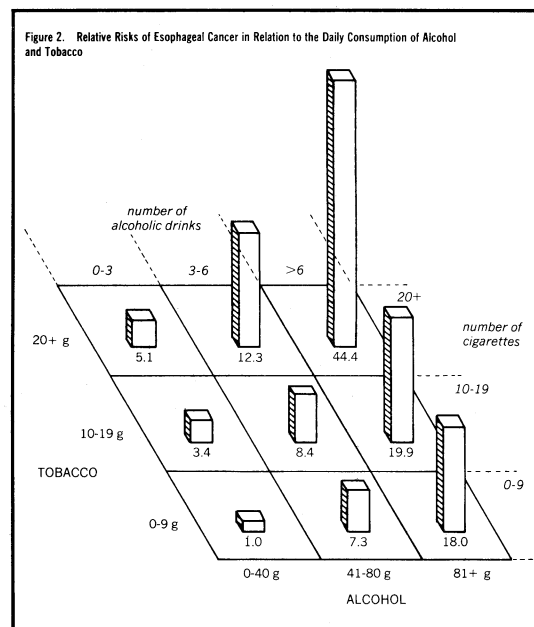
Overall, the report suggests that alcohol abuse is far from under control. "This report documents the reality that problem drinking is threatening or damaging or destroying the lives of literally tens of millions of Americans," says HEW Secretary Joseph A. Califano Jr. In addition to contributing to liver and heart disease, "indisputably, alcohol is one cause of cancer," according to the report. However, that conclusion is based on rates-of-incidence studies, and experts note that no direct cause-effect relationship between alcohol and cancer has been established.

Drinking "exposes the drinker to an increase in the risk of cancer at various sites in the body," the report states. It cites several studies indicating that drinkers run a higher risk than nondrinkers of developing cancer of the tongue, mouth, esophagus, larynx, oropharynx, hypopharynx and liver. And persons who both smoke and drink run a considerably higher risk of head and neck cancers. One French study reports that heavy smokers and drinkers have a 44.4 percent higher chance of developing esophageal cancer than do abstainers. The risk for heavy users of alcohol only is 18 times higher, and, for heavy tobacco users only, 5 times higher.

Spokesmen for the liquor industry dispute the "sweeping" conclusion that alcohol and cancer are linked. They point to a comment made earlier this year by National Cancer Institute Director Arthur C.

Upton, who stated before a U.S. Senate committee that "alcohol ingested by itself does not appear to be carcinogenic." Nevertheless, the correlations in previous studies are enough to prompt cancer and alcohol experts to discuss the phenomenon jointly this week at the National Institutes of Health.

The HEW report estimates that drinking problems cost society about \$43 billion a year in lost production, medical costs and other expenses. About half the traffic fatalities, half the homicides and one-third of the suicides are associated with alcohol misuse, according to the report, which adds that alcohol is also the third leading cause of birth defects associated with mental retardation.



Data from a study in France indicate that the risk of esophageal cancer jumps significantly as the daily rate of alcohol and tobacco consumption increases.

The figures suggest that from 1.5 to 2.25 million women have alcohol problems, but are still considerably less likely than men to develop such problems. Among the elderly, only 2 percent of the women are problem drinkers, but up to 10 percent of the men have such problems; approximately 10 percent of alcoholics in treatment are 60 or older.

"Among all special population groups in the United States, American Indians have the highest reported frequency of problems associated with drinking," the report says. Problem drinking also tends to occur more often among Spanish-speaking people, according to HEW. Drinking rates for white males and females are slightly higher than those for blacks.

"Excessive consumption of alcohol takes a terrible toll on the health, safety and happiness of millions of Americans," says Califano. "We know beyond a reasonable doubt that the misuse of alcohol is an immense health and social problem." □