Mouse-to-Mouse Gene Transfer

A gene has been transplanted from bone marrow cells of one set of mice into cells that subsequently populated the bone marrow of other mice. This feat is the first successful insertion into living animals of a selected gene. In past experiments DNA had been introduced successfully only into animal cells growing in laboratory culture (SN: 10/20/79, p. 260).

While application of this technique to humans is at least three years in the future, according to Martin J. Cline of the University of California at Los Angeles, the results suggest a variety of clinical uses. The most direct application would be the transfer of drug-resistance genes into patients with cancer to allow them to tolerate higher doses of anti-cancer drugs. Another more distant possibility would be the insertion of genes to correct human genetic blood abnormalities, such as thalassemia and sickle cell anemia.

Blood-forming tissue is at present the most amenable to gene replacement in intact animals, Cline explains. It can be extracted relatively easily, manipulated in the laboratory and replaced. More important if the technique is to work in adults, the tissue must be one whose cells continue to proliferate throughout life.

The gene that was transferred between mice is one that confers on cells resistance to a particular drug, called methotrexate (MTX), which is used in cancer therapy. Methotrexate inhibits an enzyme called dihydrofolate reductase (DHFR). When a mouse has many copies of the gene for DHFR, it is able to overpower the drug.

To introduce drug resistance into a MTX-susceptible mouse, normal bone marrow cells were replaced with MTX-resistant cells. First Cline and collaborators Winston Salser, Howard Stang and Karen Mercola incubated bone marrow cells of susceptible mice with genetic material taken from bone marrow cells of mice resistant to the drug. Some of the normal marrow cells took up new DNA.

The mice that were to receive the remodeled cells were first treated with radiation to destroy the innate population of bone marrow cells. Then they were injected with a mixed population of cells, some of which had been allowed to absorb new genes. The two groups of cells could be distinguished by a chromosomal marker.

The animals were treated with MTX to encourage the growth of drug-resistant cells. By 30 to 40 days after injection, the cells that had been permitted to pick up new genetic material clearly predominated in the bone marrow. The drug treatment had favored proliferation of the "transformed" cells.

Counts of blood cells revealed that the mice that received cells containing the new genes restored bone marrow cells more successfully in the presence of MTX than did animals injected with cells that did not contain new genes. The scientists measured the enzyme DHFR in the animals that had received the new genetic material and found it present in more than twice the normal amount.

"The studies indicate that mice receiving marrow transformed with MTX-resistant DNA tolerate high doses of MTX for longer periods of time with nearly normal haematological [blood] parameters," Cline and collaborators say in the April 3 NATURE.

Because the DHFR gene is present in low levels in normal bone marrow cells, however, one could argue that perhaps the drug resistance is due not to genes transferred but to reproduction of a gene already present in the cells (SN: 12/16/78, p. 421). To address that objection, Cline and colleagues did another set of experiments in which they inserted a different gene, one obtained from a virus, into mouse bone marrow cells. Cells containing that viral gene are also favored in the presence of MTX. The cells, inserted into irradiated mice, did produce spleen cells containing the viral gene. These experiments clearly demonstrated that a gene had been transplanted.

Genes for drug resistance will probably be required in future attempts to transfer genes having other functions. Most genes, even if they could cure a genetic disease, would not give any selective advantage among proliferating cells. The researchers suggest that to transfer such a gene it be linked to a gene that does give an advantage under selected conditions. "Drug-resistance genes are natural candidates for this role," they conclude.

In discussion accompanying the NATURE article, Bob Williamson of St. Mary's Hospital Medical School in London points out that scientists still face the problem of guaranteeing correct control over transplanted genes. He says that transplanted genes must be inserted into the "correct" place on the chromosome or other methods must be found to ensure balanced gene expression before gene therapy becomes "a real possibility." □

Me Tarzan, you IBM System/370 Model 168

According to one chapter in the apocrypha of technology there once was an elevator in a certain New York department store that had a programed system for talking to customers who blocked the closing of its doors: "Please clear the doors....Clear the doors or we don't move. ...Get out of the way you meshugginneh @%&¢#[." If the customers cursed back, there is no report that the doors understood.

At the IBM Thomas J. Watson Research Center in Yorktown Heights, N.Y., on the edge of the Big Apple's metropolitan district, they have developed a computer that does understand spoken English as it might be naturally spoken — that is, it is not restricted to a series of preset command phrases carefully pronounced. The computer's recognition vocabulary is limited, for now anyway, to 1,000 words. Philosophers would feel constricted, but this compares favorably to the size of the vocabulary of Basic English, a dialect that was once promoted for business communication in the multilingual South Pacific.

Frederick Jelinek, who leads the research group, told a recent meeting of the Society of Automotive Engineers: "...We are now working on the recognition of continuous speech, without the aid of artificial pauses between words or artificial constraints, but with a limited vocabulary. ... Ours is the only place in the United States and, as far as we know, the world, where speech recognition experiments of such complexity are being attempted." Lalit Bahl, Raimo Bakis, Paul Cohen, Alan

Analysis of sentence into 340 spectral time samples (vertical lines on graph).