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." □

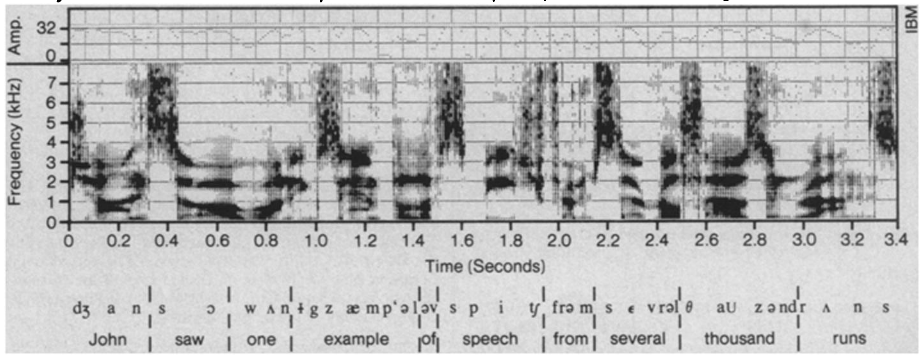
Me Tarzan, you IBM System/370 Model 168

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).



Cole, Burn Lewis, Robert Mercer, Eva-Maria Muckstein, Arthur Nadas and Lenore Restifo join Jelinek in the work.

In the experiments an operator sits in a "quiet room" and reads the computer sentences made from the words in the 1,000-word vocabulary. After a delay, which can be quite long, the words appear on a fluorescent screen. The computer has to be trained to understand the speech idiosyncracies of a particular operator, a procedure that takes about two hours and involves the reading of 900 test sentences made out of the 1,000 words.

The vocabulary comes neither from baby talk nor Tarzan talk but from the language of lawyers submitting patent applications for laser devices. Shakespeare or Bertrand Russell might have thought 1,000 words inhibiting, but patent lawyers can produce some involved sentences out of them. Here is one of the 900 test sentences: "After a period of time, the dye in the switching cell will decay and not be as effective in its switching operation."

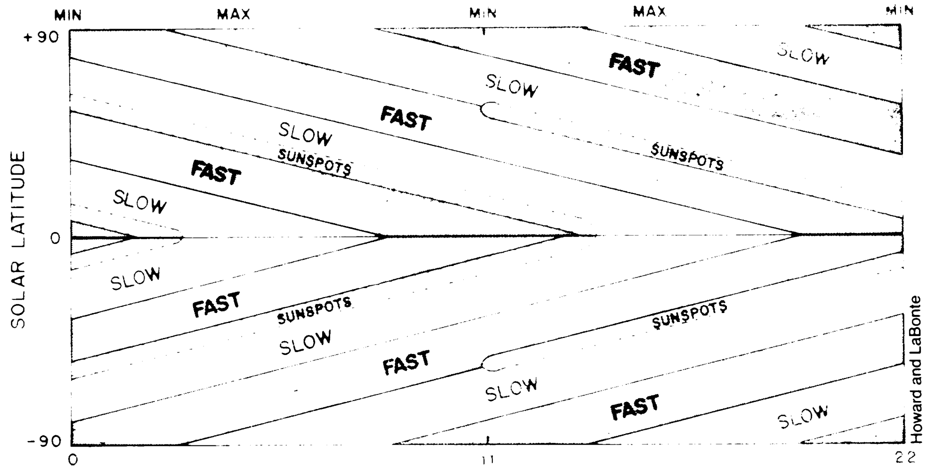
The computer can recognize more than the 900 test sentences. The probable sequences of different classes of words — articles, nouns, verbs, adjectives, etc. — according to English grammar are in its memory. It can use these rules to analyze unfamiliar sentences provided they are made up of the 1,000 words.

The machine works by using an acoustic processor to sample the wave pattern of the speaker's voice 20,000 times a second. The information in the sample is digitized. A thousand samples are collected at a time and put through the procedure called discrete Fourier transform, which involves adding, subtracting and integrating waveforms to produce a useful synthesis of the information over time. This yields characteristic patterns known as spectral time samples, 100 of them every second. The computer compares these with 200 prototypes stored in the processor's memory during the training session with the particular speaker. The processor classifies the time samples according to the sounds in the original word. As the acoustic processor puts them out, a linguistic decoder matches the classified sound patterns to the most probable sentence pattern they seem to fit.

This procedure can lead to mistakes, but they sound more like human mistakes than the gibberish that usually results from computer foul-ups: The speaker says: "Although the invention has been described. . . . " The computer writes: "All of the invention has been described." Response time is very slow, however. A sentence uttered in 30 seconds may take the computer 100 minutes to display.

Plans for the future include increasing the flexibility of the device by lowering training time for new operators to 15 minutes, quickening response time until the response comes in real time, and increasing the machine's vocabulary. That would result in a useful dictation system. □

Solar currents and the magnetic cycle



Fast currents form every 11 years, travel to equator. Sunspots form at boundaries.

Solar observers have long noted that the sun has a 22-year magnetic cycle: Magnetic events, such as sunspots, flares and prominences, as well as reversals in the polarity of the field, appear to follow this schedule. Less clear and much debated has been whether the cyclic behavior is only surface deep or the result of a magnetic churn far below the sun's dermis.

Now, astronomers at Hale Observatories in California have evidence that such activity is due to deep motions of the sun's interior. The researchers, Robert Howard and Barry LaBonte, have observed bands of fast and slow currents on the sun's surface that originate at the poles and drift in a 22-year journey toward the equator. Furthermore, Howard told a press conference last week, the currents appear associated with the development of sunspots. "What we see is a large-scale, deep-rooted oscillatory motion of the sun that some way causes the cycle to happen. . . . It is the first time evidence has been found for motion below the surface of the sun associated with the solar cycle."

Early astronomers observed that the equator of the sun's gaseous orb rotates from east to west faster than do its poles — once every 25 days, compared with once every 33 days. Using the Mount Wilson facility operated by California Institute of Technology and the Carnegie Institution of Washington, Howard and LaBonte attempted to see if the rate of rotation was constant at a given latitude across the sun. By measuring the shift in the wavelength of iron, the researchers charted the daily velocities of 24,000 points on the sun's surface during the period between Jan. 15, 1968, and Dec. 28, 1979. When the velocities were plotted according to latitude, the researchers found that certain zones moved about 3 meters per second (7 miles per hour) faster than the average rotation of the sun and others moved 3 meters per second slower than the rest of the sun.

In each solar hemisphere, Howard says, there are four zones of alternating speed, two fast and two slow, and the currents are arranged symmetrically about the solar equator. Like the stripe of red that seems to move down a rotating barber shop pole, a fast current originates at the solar poles every 11 years and begins a 22-year trip toward the equator. When the fast zone is about midway to its destination, sunspots begin to appear on the poleward boundary between the fast zone and the slow zone next to it. The sunspots then travel with the fast current to the equator, where both disappear. The fast and slow currents associated with the upcoming cycle of sunspot activity are already discernable at high solar latitudes, Howard said, but sunspots will not appear for eight years. "This is the first time we have been able to actually see the motions associated with the next solar cycle."

Because of the regularity and large size of the features, the global nature of the phenomenon and the identical hemispheric patterns, Howard and LaBonte conclude that the currents are driven by oscillations of a magnetic field that is deep within the sun. Previously regarded by many as the primary and possibly the driving event of the magnetic cycle, Howard and LaBonte's observations make sunspots "just the flotsam and jetsam of deep-seated oscillations." They may arise, Howard suggests, as the magnetic field lines beneath the currents are stretched by the motion of the currents, become amplified and erupt to the surface. Howard and LaBonte's work "is evidence for a magnetic field that is generated rather deeper and more regular than previously thought," says Princeton University solar physicist R. H. Dicke. The work "will constrain theorists to a model based on motions below the surface," says John Wilcox of the Stanford Solar Observatory, adding that his group is now attempting to confirm the discovery. The finding does not explain the sun's magnetic cycle, says Howard, but "we know now how to attack the solar cycle." □