good offices of the NAS, the traditional agent for international scientific trips and exchanges. The Chinese have indicated that they will not deal directly with the Academy until China-U.S. relations are "normalized," which apparently means not until formal diplomatic relations are established.

The concluding speaker of the meeting was John H. Knowles, general director of Massachusetts General Hospital, a member of the institute, and the next president of the Rockefeller Foundation. Knowles gave an iconoclastic analysis of medical education, physician manpower, and health insurance and challenged the institute to come to grips with such problems lest it become merely a "status organization."

The new institute has set out to influence major decisions in the health field. Hogness himself has reportedly made a start by contributing, along with representative of the Association of American Medical Colleges (AAMC) and others, to Representative Paul G. Rogers' (D–Fla.) development of the House alternative to the Senate's version of the big new cancer research program (*Science*, 22 October). The institute plans to cultivate cooperative links with other national organizations in the health field, such as the AAMC and the American Medical Association, but obviously expects that the spectrum of professions represented in its membership will give it important advantages over more narrowly based organizations. Only the next few years will tell, however, whether the institute will be just, as one member of the audience surmised, "another competitor for funds," or whether it will really carve itself a special niche in the burgeoning ecology of health policy and politics.

—JOHN WALSH

APPOINTMENTS

Robert G. Layer, chancellor, Southern Illinois University, Carbondale, to president of the university. . . . **Edward J. McCarthy**, former president, Biscayne College, to president, Villanova University. . . . **Stanley E. McCaffery**, president, San Francisco Bay Area Council, to president, University of the Pacific. . . . **John H. Ehrenreich**, chairman of watershed management, University of Arizona, to dean, College of Forestry, Wildlife, and Range Sciences, University of Idaho. . . . **Merle L. Borrowman**, dean, School of Education, University of California, Riverside, to dean, School of Education, University of California, Berkeley. . . . **Joseph M. Pettit**, dean, School of Engineering, Stanford University, to president, Georgia Institute of Technology.

RESEARCH TOPICS

Molecular Biology: Gene Insertion into Mammalian Cells

The problem of inserting specific genes into human cells has intrigued molecular geneticists, and the prospect of the successful solution of this problem has concerned everyone. Both the excitement and the concern have grown now that the armchair speculations—and exploratory results—of a few years ago have matured into hard experimental work. The current results of that work indicate that animal viruses, bacterial viruses, and cell fusion techniques are all capable of introducing new functional genes into mammalian cells, although many of the fundamental genetic and regulatory processes in mammalian cells remain unknown.

Much has been learned about the genetic code and the mechanisms of the replication of DNA, the transcription of DNA into RNA, and the translation of RNA into protein, especially in bacterial cells. A clever and sufficiently industrious molecular geneticist can often produce a specific mutation in any of a large number of genes in the bacterium *Escherichia coli*, can delete genes or add new ones from outside the cell, and can then regulate the expression of genetic traits inside the cell. But the extension of these techniques from bacteria and bacterial viruses (bacteriophages) to nucleated (eukaryotic) cells, especially human cells, awaited new tools and more knowledge.

Several biologists have studied the interaction of foreign DNA with nucleated cells. Among these, Pradman Qasba and Vasken Aposhian at the University of Maryland School of Medicine in Baltimore, have recently shown that one type of animal virus can be used to transport DNA from mouse cells into the nuclei of human cells. At the Roswell Park Memorial Institute in Buffalo, W. Munyon and his coworkers have shown that another type of animal virus may have inserted a specific gene into mouse cells without harming the cells. These workers found that the enzyme specified by this gene was made by the cell and that the new gene seemed to be replicated as the cells divided.

Munyon and his group infected mutant L cells (a line of mouse tissue culture cells) that lacked the enzyme thymidine kinase with the animal virus herpes simplex. The virus had been irradiated with ultraviolet light to decrease its ability to kill cells (*1*). Herpes simplex virus normally induces a thymidine kinase activity during infection before it kills the cells, but in this experiment about 0.1 percent of the infected L cells were transformed by the irradiated virus into stable cells that had thymidine kinase activity and were maintained in culture for 8 months. No measurable proportion ($< 10^{-8}$) of control L cells gained the ability to express thymidine kinase when uninfected cells or cells infected with a herpes simplex mutant that does not induce thymidine kinase activity were examined.

These results are consistent with the idea that the herpes simplex virus introduced a gene for thymidine kinase into the L cells and that this gene was then maintained and replicated by the cells. However, Munyon notes the possibility that a herpes gene product may have simply induced the stable expression of a gene that was already present in the L cells.

Aposhian has proposed that pseudo-

virions—which consist of normal virus' protein coats that have enclosed foreign pieces of DNA—might be able to deliver foreign genes into another cell, and that these new genes could function and be replicated in the cell. Qasba and Aposhian have now established that pseudovirions of an animal virus, polyoma, containing labeled DNA from mouse embryo cells can deliver this DNA inside the nuclei of human embryo cells in the form of uncoated pseudovirion DNA as soon as 24 hours after infection of the human cells by the polyoma pseudovirions (*2*). At present no actual expression or replication of any newly introduced genes has been shown in this system, but many workers think it likely that uncoated mammalian DNA in a mammalian cell nucleus is capable of integrating itself into the host chromosome and functioning in some way.

Carl Merril and his co-workers (*3*) at the National Institutes of Health in Bethesda have taken a different approach. They have shown that a bacteriophage is capable of introducing a selected functional gene into human cells. Merril had worked with the bacterial virus lambda phage, one of the transducing phages of *E. coli*. Transducing phages have been among the most useful genetic tools available to molecular biologists. Sometimes bacterial genes are included in the DNA of the new phage produced during infection of a bacterium by a transducing phage. If these phages infect another bacterium they can transduce the bacterial genes that they carry into their new host. In this way transducing phages are often used to selectively introduce new functional genes into bacteria.

The genetic structure of lambda has been very well mapped, and a number of remarkable lambda transducing phages (that is, lambda that carry bacterial genes) are available. Merril's group decided to attempt the transduction of cultured human fibroblast cells from the skin of a patient with galactosemia, the disease that results from an inborn error of metabolism in which the enzyme α-D-galactose-1-phosphate uridyl (GPU) transferase is lacking. The cultured fibroblasts were treated with lambda phage (λ pgal) that carried the *E. coli* galactose operon—a set of genes that codes for the enzymes which convert galactose to glucose and controls their synthesis.

Merril and his co-workers hoped that the GPU transferase gene, which is part of the galactose operon, could be supplied to the fibroblasts by λ pgal and that the fibroblasts would use this transduced gene to make the GPU transferase enzyme.

These expectations were fulfilled. Infection of the fibroblasts by λ pgal resulted in both the production of lambda-specific RNA and in the appearance of GPU transferase activity in the fibroblasts. The lambda-specific RNA and the new GPU transferase activity were found in significant amounts and persisted at the same amounts per cell for more than 40 days (during which more than eight doublings of the cells took place). In addition, uncoated λ pgal DNA was, in Merril's experiment, at least as effective as the whole virus particle. Control infections by normal lambda and by λ pgal with a mutation that inactivates its transferase resulted in the production of lambda-specific RNA but not in transferase activity.

There is still no evidence to indicate what part of the cell houses the lambda DNA. But the experiments performed by Merril's group have shown that lambda DNA can enter human cells, and once there at least some of its genes can be replicated, transcribed, and translated.

Cell Fusion Techniques

Viruses are not the only means of introducing new genes into mammalian cells, however. Henry Harris' group at Oxford in England has now shown that cell fusion can also be used to insert a functional gene from chicken cells into mouse tissue culture cells (*4*). If two cells are fused or if another nucleus is introduced into a cell, the dividing time of the resulting multinucleate cell is primarily determined by the nucleus that is closest to division. The other nuclei may be forced to divide before they are ready, and their chromosomes usually undergo a "premature condensation" which results in their fragmentation or "pulverization."

The Harris group fused chick red blood cells, whose nuclei carry the gene for chick inosinic acid pyrophosphorylase, with mouse fibroblast A_9 cells, which are a mutant line of mouse L cells deficient in this enzyme. During cell division, the nuclear membranes in these hybrid cells disappear, and the chick chromosomes undergo pulverization. Although only mouse nuclei appeared in the daughter cells after mitosis, some (2×10^{-5}) of the daughter cells had gained the ability to synthesize chick inosinic acid pyrophosphorylase. However, after more than 100 generations in culture, 20 percent of these transformed hybrid cells lost the ability to make this enzyme, as compared to 1 out of 10^6 in a normal L cell population. Hence the chick gene for inosinic acid pyrophosphorylase was replicated and remained functional in the mouse cells, although it was not as genetically stable as the normal mouse gene for this enzyme. This experiment did not provide direct evidence for the location of the chick gene inside the mouse cells, but indirect evidence leads the Harris group to name the mouse nucleus as its probable residence.

A number of laboratories are already extending these gene transfer techniques. Aposhian's group is now studying the genetic properties of polyoma pseudovirions in mice. They are also attempting to produce polyoma pseudovirions containing the gene for human thymidine kinase. Merril has infected whole animals with transducing lambda bacteriophage in order to determine whether any new traits gained by the animals from the genes that are transported by the phage can be inherited from one generation to the next.

The ability to transfer small segments of DNA from one cell to another gives molecular geneticists the opportunity to map the locations of genes within mammalian chromosomes. In turn, understanding the method by which genes are organized into functional units within the chromosome may reveal how the regulation of gene expression takes place. This regulation may play an important role in the differentiation of animal cells.

Current developments certainly do not yet add up to "genetic engineering"; but there now exists very strong evidence, with a number of different techniques, that experimenters can transfer genes between, and insert them into, mammalian cells—a development that opens to experiment many questions about gene function in animals and in humans. Now that a few of the basic tools of molecular genetics have been extended to mammalian cells, more than a few biologists share Aposhian's concern that science "will give us gene therapy before society is prepared for it."—DANIEL RABOVSKY

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