Mintz says, "These individuals are the perfect model of a new strain. You can produce mice essentially engineered in a dish. You only need one germ line animal with the desired change to perpetuate a new strain."

Mintz thinks that the capabilities of experiments with the cultured teratocarcinoma cells will partly overlap those of methods in which cloned genes are injected into fertilized eggs, which have also been yielding very encouraging results. This recent work was foreshadowed by experiments done in 1974, before cloned recombinant DNA was available, by Mintz and Rudolf Jaenisch, who is currently at the Heinrich-Pette Institut in Hamburg. They showed that DNA from a virus (SV40) could be injected into embryos and retained throughout development.

A few months ago, Mintz, Stewart, and Wagner reported that embryos that developed from fertilized eggs which had been injected with the linked genes for thymidine kinase and human β-globin carried intact copies of both genes. One of the embryos made large quantities of thymidine kinase.

Soon after this report came four more showing that foreign genes, when injected into fertilized mouse eggs, could enter the germ lines of the resulting animals and be transmitted to their progeny. In two cases the investigators injected rabbit globin genes. One of these groups included Thomas Wagner of Ohio University and Peter Hoppe of the Jackson Laboratory; the other consisted of Franklin Costantini and Elizabeth Lacy of the University of Oxford, England.

In the remaining two cases the investigators injected the viral gene for thymidine kinase. These experiments were performed by researchers from the laboratories of Ralph Brinster at the School of Veterinary Medicine of the University of Pennsylvania and Richard Palmiter of the University of Washington and by Jon Gordon and Frank Ruddle of Yale University. The Wagner-Hoppe and Brinster-Palmiter groups reported that the injected genes produced their protein products in some of the animals that developed. Mintz, Stewart, and Erwin Wagner have now also found transmission of injected gene sequences to progeny.

Comparing the egg injection method with the use of teratocarcinoma cells, Mintz says, "In both cases you can introduce an intact or manipulated gene. The egg injection route has the advantage that with luck you can get the DNA into all the cells at once. But the teratocarcinoma route has the advantage that you can preselect the positive cells and characterize them with regard to the state of the gene you introduce."

In addition to their use to study the molecular biology of development, Mintz thinks that the methods may make possible the production of laboratory animal models that can be used to investigate human genetic diseases for which such models are now lacking. Mice having Lesch-Nyhan syndrome, a severe neurological condition caused by a single defective gene, or the thalassemias, which are anemias caused by defective globin genes, are two examples.

Within the past 2 to 3 years researchers have made rapid progress toward the ability to produce mice with hand-tailored genes. As Mintz sums up the situation, "I think it is exciting, what is happening in this area. It's great being alive in science today. I would hate to have missed this."—JEAN L. MARX

Additional Reading

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Alzheimer's Research Poses Dilemma

Legal and ethical issues in obtaining informed consent are particularly thorny because patients are senile

Alzheimer's disease afflicts 1.5 to 2 million Americans, causing a progressive and irreversible senility, starting with memory loss for recent events and continuing to a point where most patients cannot feed themselves, no longer recognize their families, and do not even know their own names. These patients also have life expectancies that are one-half to one-third those of healthy persons of the same age, according to Robert Katzman of the Albert Einstein College of Medicine. "We're dealing with a disease that is in many ways as malignant as cancer," Katzman says.

In recent years, medical scientists have found clues to what might cause the symptoms of Alzheimer's disease and what treatments might help. In particular the neurotransmitter acetylcholine is not as abundant as it should be in the brains of these patients (*Science*, 6 March 1981, p. 1032). But now researchers are confronted with a difficult legal and ethical problem. How can they obtain informed consent to do research on these patients? All too often, the patients themselves cannot give consent. As Hilda Pridgeon, the wife of an Alzheimer's disease patient and a founder of the Chicago-headquartered Alzheimer's Disease and Related Disorders Association, explains, "By the time you know a patient has Alzheimer's disease, the patient can't deal with intangibles. They're down to dealing with how to brush their teeth or take a shower."

The National Institute on Aging held a meeting* to discuss the ethical and legal questions relating to research on Alzheimer's disease patients. The central issue, as Andrew Jameton of the University of California in San Francisco says, is that "We're in a bind. We're interested in doing research on exactly the group that, according to our notions of voluntariness and informed consent, we shouldn't do research on."

The sorts of research that are causing the most concern are invasive procedures offering no therapeutic benefits to patients. To take the most emotionally charged example, there was discussion at the meeting of doing brain biopsies on patients before enrolling them in clinical studies in order to be sure they really have Alzheimer's disease. As many as 30 percent of patients thought to have Alzheimer's on the basis of their clinical

*The conference on "Senile Dementia of the Alzheimer's Type and Related Diseases: Ethical and Legal Issues Related to Informed Consent" was held on 23 and 24 November.

0036-8075/82/0101-0047$01.00/0
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symptoms are misdiagnosed. If researchers could get a small sample of brain tissue from a patient's right frontal cortex, they could see if the brain had the plaques and neurofibrillary tangles that are characteristic of the disease. Brain biopsies have a low complication rate, according to Christine Cassel of the Veterans Administration Medical Center in Portland, but if complications do occur, they can be serious. The most likely complications are infection and bleeding in the brain.

Kenneth Davis of the Veterans Administration Medical Center in New York described another kind of invasive and nontherapeutic research. He recently gave intravenous infusions of physostigmine to ten Alzheimer's disease patients and found that this drug, which increases brain acetylcholine concentration, can improve patients' ability to learn new things. Since physostigmine is active for only a few minutes, the study could not possibly benefit the patients. But the work does have some consequences for future research, Davis says, because it indicates that a longer-acting derivative of physostigmine might be a useful treatment. He emphasizes that the ten patients were studied early enough in the course of the disease so that, at least by some definitions of competence, they were able to give consent.

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This does not mean that it is always most appropriate to study patients early in the course of the disease. Davis explains that "There are certain questions that can only be answered by research with patients that are incompetent. It is only in cases of advanced disease that we see certain problems, like aphasia [loss of the ability to use or understand words], incontinence, disorientation, and apraxia [forgetting how to make certain muscle movements]. If we want to study these problems, we will have to use incompetent patients."

But when there are questions about patients' competence to give consent, who decides if research can go on? Robert Schwartz, a University of New Mexico lawyer, explains: "Informed consent is not just the Golden Rule in another guise. Informed consent tells researchers: Do unto others as they would have you do unto them." The problem is that when a patient can no longer remember his own name or recognize his own doctor, it is virtually impossible to determine what that patient would have wanted done to him.

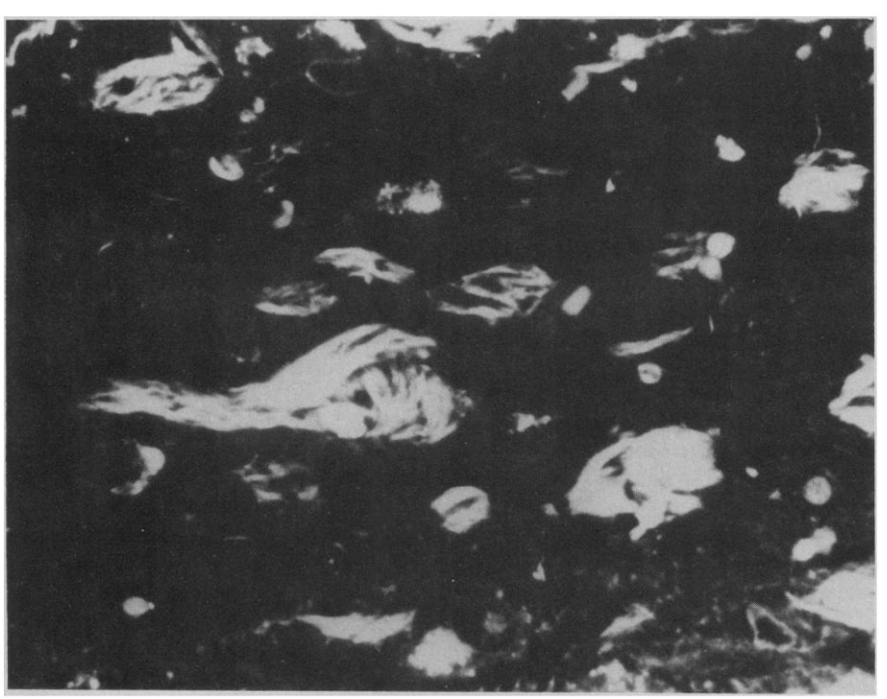
Most researchers, including Davis, have asked relatives for permission to enroll patients in research studies when there are questions about whether the patients themselves can give consent. But Nancy Dubler, an attorney in the department of social medicine at Montefiore Hospital in New York, says that she does not think that such consent would hold up in court, especially if the patients themselves would not be helped by the research. "At this point, given the state of the law, I don't see a way to do research with no possibility of therapeutic benefit," she says.

One suggestion, which got a lot of attention at the meeting, was for Alzheimer's disease patients to designate, at the time they are diagnosed, someone to decide for them whether they can participate in research when they become incompetent. But, says Davis, "Although a penultimate will obviously would be a great advantage, if we wait to do our research until patients come who have made penultimate wills, we may find ourselves waiting for Godot."

Cassell, a gerontologist and ethicist, says she is afraid that in their great concern to protect Alzheimer's disease patients, investigators and lawyers may overprotect them and prevent them from benefiting from research. "One reason you don't want to limit research too much is that when you do research on patients they are suddenly considered interesting. A problem with senile patients is that they are put in nursing homes and ignored. If they suddenly become 'interesting' to doctors, they get more attention and many aspects of their care improve."

Perhaps the real problem is that the very idea of doing nontherapeutic research on incompetent patients clashes with the value system in this country. Alan Weisbard, a lawyer with the President's Commission for the Study of Ethical Problems in Medicine and Biomedical Behavioral Research, puts it this way: "What you are asking is for American society to please acknowledge that we want to use people in research for the benefit of others. Our society has had a great deal of trouble accepting that."

—GINA KOLATA



Albert Einstein College of Medicine

Plaques and tangles in the brain of an Alzheimer's disease patient