Poinar says.

The paleofeces findings show that prehistoric American diets were "incredibly diverse," Sobolik says. One paleofeces alone contained remains of four kinds of animals and three plants, while another had two animals and four plants. If archaeologists and molecular biologists work together, Poinar says, "we get a more complete picture of what the hunter-gatherers ate."

Next the team hopes to track diet over time. "There was a continual flow of dung over 8000 years," Poinar notes. Previous studies indicate that diet changed little over those centuries, a hypothesis that DNA may be able to test. For instance, the researchers might be able to detect changes in big game abundance. And two other caves nearby also contain ancient dung. The hunter-gatherers are thought to have switched caves during different times of the year to exploit different resources, such as fall acorns in the upland forests. If so, the paleofeces might reveal seasonal changes in diet.

What many archaeologists would especially love to know, however, is the sex of a defecator. This could provide insights into dietary differences between males and females, Sobolik notes. She and others have attempted to determine the sex in some paleofeces by the ratio of testosterone and estradiol. Analysis of nuclear DNA, of course, would give a much less ambiguous answer. Nuclear DNA is harder than mitochondrial DNA to amplify, because it is so much scarcer, but Poinar says he is working on it.

Hunting a Mammoth Killer

Last year, molecular biologist Alex Greenwood and his colleagues at the American Museum of Natural History (AMNH) in New York City prised the first sequences of nuclear DNA from an extinct species, the woolly mammoth. Now they are hoping to use the mammoth as a vehicle for pioneering a new field: paleovirology.

As a first foray into the relatively uncharted area of ancient viral genetics, Greenwood announced at the meeting that his group had managed to pull out of a mammoth cell's nucleus partial sequences of a class of endogenous retroviruses (ERV). An ERV is born when a retrovirus sneaks into an egg or sperm and sets up camp in its DNA. This has happened many times in all creatures, from yeast to people. Because ERV sequences—some of which are thought to have maintained their activity or acquired functions—appear to be strongly conserved in living mammals, experts caution that ancient sequences probably don't represent a potential gold mine of new information on viral evolution.

That's fine, because Greenwood and his AMNH colleagues have bigger game in mind. They want to probe a novel idea about what might have driven mammoths, giant ground sloths, and other large mammals to extinction in North America at the end of the last ice age. The two leading ideas are that rapid climate change sharply curtailed food supplies and shrank populations below sustainable levels, or that overhunting by early Americans did the job. The new idea comes from AMNH mammalogist Ross MacPhee and virologist Preston Marx of the Aaron Diamond AIDS Research Center in New York City, who in 1997 proposed that pathogens brought across the Bering land bridge by humans or commensals such as dogs jumped into mammoths with the infectivity of the flu and the lethality of Ebola. Although the idea is provocative, the researchers know of no modern pathogen that would fit this description—thus complicating any hunt for such a shadowy rogue.

CREDIT: CLARE FLEMMING/AMERICAN MUSEUM OF NATURAL HISTORY

Big game. Discovery of ancient DNA in mammoth bones like this humerus has launched a quest for deadly ice age pathogens.

That doesn't mean it's not worth searching for evidence of a so-called "hyperdisease." Woolly mammoth flesh—sometimes even whole carcasses—is found deep-frozen in permafrost in Alaska and Siberia. MacPhee's team has collected samples from Alaska, mainland Siberia, and Wrangel Island in the East Siberian Sea. Tissue from individuals ranging in age from 26,000 years to 4500 years was well enough preserved to yield nuclear DNA sequences, which were published last November in *Molecular Biology and Evolution*. This was the first proof that it's possible to extract single-copy nuclear DNA from extinct animals. This kind of DNA is much rarer than the plentiful DNA of mitochondria, the miniature powerhouses inside animal cells that have their own genome.

Finding a pathogen lurking in frozen mammoth tissue will be much trickier. Their DNA may be even scarcer than native mammoth DNA, and the pathogen may not have infected bone, the most common fossilized tissue. "It is mostly a matter of luck," says Greenwood. "You have to find an infected individual who had a high enough viral load that is detectable."

Greenwood and MacPhee plan to search mammoth remains before and after humans arrived in North America. If they find viruses or bacteria only in the younger samples, it would support the notion that humans or their domesticated beasts brought diseases that doomed the mammoths. "If they find an exogenous virus," says retrovirus expert Robin Weiss of University College London, "then I'll sit straight upright." **–ERIK STOKSTAD**

DIABETES RESEARCH

Islet Transplants Not Yet Ready for Prime Time

Although recent highly publicized transplantation results are promising, lack of islet tissue will limit the procedure's availability for years

When researchers in Edmonton, Canada, announced last month that a new procedure for transplanting pancreatic islet cells had freed seven adults with type I diabetes from taking insulin, the news got front-page treatment around the world. Because of the potential therapeutic implications of the work, *The New England Journal of Medicine* lifted the embargo on a paper detailing the results of the procedure, known as the "Edmonton Protocol," releasing it on 6 June—more than 7 weeks before its scheduled publication date of 27 July.

News stories touted the findings as the beginning of the end of life with syringes for the more than 1 million Americans with type I (or "juvenile") diabetes. And on 13 July, President Bill Clinton took a break from peace talks between Palestinian and Israeli leaders to announce a mostly federally funded $5 million study aimed at replicating the Edmonton team's results that will be carried out at 10 centers in North America and Europe. But impressive as the Edmonton group's achievement was, some important caveats tended to get lost in the public enthusiasm.

A big drawback is that transplant recipients would need to take immunosuppressive

drugs for the rest of their lives to keep from rejecting the tissue. But even if the benefits of the transplants outweigh the risks of the drugs, transplant surgeons—including members of the Edmonton team itself—point to an even bigger problem: There's just not enough islet tissue to go around and there won't be anytime soon. "It's clear that [the Edmonton study] is progress. [But] I think it's years before they have a practical application," says David Harlan, head of the transplantation and immunity branch at the National Institutes of Health in Bethesda, Maryland.

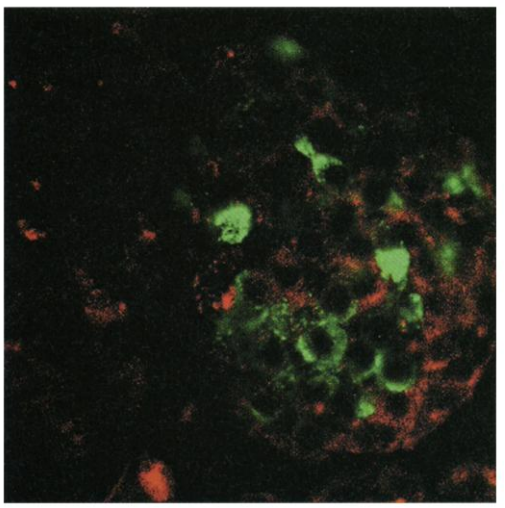
Currently, islets are obtained from the pancreases of cadavers, and less than 6000 suitable pancreases become available each year, according to the United Network for Organ Sharing. Because it takes more than one pancreas to provide enough cells for a single transplant, that's not enough to make a dent in the problem. The Juvenile Diabetes Foundation estimates that more than 30,000 new cases of type I diabetes are diagnosed annually. Although efforts are under way to develop new sources of islet cells—growing them in the lab from stem cells and other sources—such cultured cells are still years away from human testing. "Our program now is really limited by our ability to get [islet] tissue," says Jonathan Lakey of the University of Alberta in Edmonton, one of the surgeons who treated the original seven patients.

Type I diabetes develops when the beta cells of the islets stop producing insulin, possibly because they are destroyed by an autoimmune attack. Researchers have been trying for years to treat the disease by transplanting islet tissue or the beta cells themselves. Aside from sparing patients the discomfort and inconvenience of daily insulin shots, allowing the body to produce its own insulin via the transplants may provide better control of blood glucose concentrations and might thus lower the risks of blindness, kidney failure, and other possible complications of diabetes.

Results have generally been dismal, however, mainly because islet cells are extremely fragile. Researchers had a hard time obtaining enough tissue to make a difference, and it often didn't survive transplantation. Even the steroid drugs used for immunosuppression in these earlier efforts tended to kill the beta cells.

The Edmonton investigators overcame these problems in part by eliminating steroids from their postsurgery treatment protocol in favor of newer, less toxic immunosuppressive drugs. Even so, they needed two donated pancreases to isolate enough functional islets to make each of the transplants successful. One of the original seven patients told *Science* that he was called in to the operating room and prepped eight times only to be told that not enough functioning islets could be isolated from the single donated pancreases then available.

The demonstration that islet transplantation can be effective has provided further impetus to efforts to find ways to mass-produce insulin-producing cells in the laboratory. For example, Susan Bonner-Weir's team at the Joslin Diabetes Center at Harvard Medical School in Boston reported in the 5 July issue of the *Proceedings of the National Academy of Sciences* that they had grown isletlike groups of cells from the usually discarded duct cells of donated human pancreases.



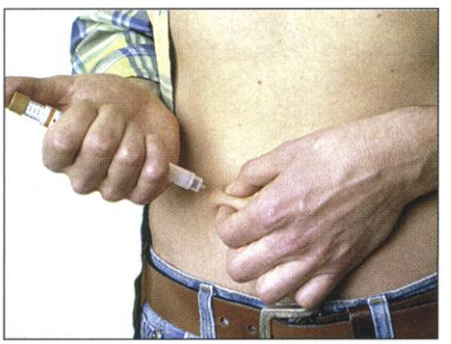
Future therapy? Someday, cultured cells from islet buds such as this one (red staining indicates insulin and green staining glucagon) may make insulin injections *(right)* obsolete—but not yet.

The cells, dubbed cultivated human islet buds or CHIBs, produce insulin in response to glucose. So far, however, the technique only produces about 30,000 CHIBs from the duct cells of one pancreas, whereas most patients in the Edmonton Protocol received something in the neighborhood of 700,000 islets. "It's a drop in the bucket compared to what you need for Edmonton," says Bonner-Weir. Her team is working on ways to boost the output of CHIBs, and it has begun testing the cells in mice with an experimental form of diabetes. But Bonner-Weir estimates that it will be at least 3 years before CHIBs are ready for human trials.

Other investigators have abandoned complex islets and gone right to the insulin-producing beta cells. The cells grow easily in lab culture, but previous efforts to produce them for transplant failed because they stop producing insulin when they are cultured in the lab. Last month, however, molecular geneticist Fred Levine and his colleagues at the University of California, San Diego (UCSD), Cancer Center announced that they had reactivated glucose-responsive insulin production in beta cells grown from immortal cell lines.

When the researchers transplanted these cells into immunodeficient, diabetic mice, the animals maintained normal blood glucose levels for up to 3 months. Still, the UCSD group has only put its beta cells through about 100 doublings, producing just "a tiny fraction of the numbers we would need for any industrial production," Levine warns. The researchers are currently trying to boost cell production levels, but even with the most optimistic scenario, Levine adds, human clinical trials are 5 years away.

Embryonic stem cells offer another promising source of beta cells. Earlier this year, Bernat Soria and his colleagues at the Institute of Bioengineering at Universidad Miguel Hernandez in San Juan, Spain, reported that they had not only produced beta-



like cells from mouse embryonic stem cells, but that the cells "cured" diabetes for more than 1 year after they were transplanted into genetically altered mice.

Embryo-derived beta cells seem to produce insulin no matter how many times they have divided in vitro, Soria says. But one drawback—aside from ethical concerns surrounding human embryonic stem cell research—is that the cells may divide so prolifically that they risk giving rise to tumors once they are transplanted. That didn't happen with the Soria team's transplanted mice, but the method is not yet reliable enough to try in humans, he says.

Ultimately, researchers may be able to solve the problems with their cultured cells and produce enough for all the diabetes patients who need transplants. Until then, says Lakey, diabetics will have to join the 70,000 other Americans who currently sit on waiting lists for organs. The Edmonton Protocol is "a cure like a liver transplant is a cure," he says. "The patients have pagers and they wait."

–TODD ZWILLICH

Todd Zwillich is a free-lance writer based in Washington, D.C.

CREDITS: (LEFT TO RIGHT) S. BONNER-WEIR, M. TENOFSKY; INDEX STOCK IMAGERY