Exhibit 12

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New Test That Finds Hidden AIDS Virus Is a Sleuth With Value in Many Fields

The technique is used in archeology, forensic science and medicine.

By HAROLD M. SCHMECK Jr.

The human brain lay for 7,000 years in a Florida spring, but scientists using a new technique grew multiple copies of its remaining traces of genetic material to help puzzle out the identity of an ancient American.

In medical laboratories, scientists using the same technique have found otherwise undetectable evidence that the AIDS virus was lurking in blood cells, a breakthrough that promises to transform testing.

Forensic experts, meanwhile, have used the technique to help solve crimes from evidence as meager as the genetic material in a single human hair.

The new laboratory technique, polymerase chain reaction, known as PCR, was developed only a few years ago, but is already having far-reaching impacts in many fields. The technique makes it possible to grow quickly many copies of a scarce piece of DNA, the genetic material of all living things. It enables scientists for the first time to identify and study extremely small traces of genetic material — to take the equivalent of the needle in the haystack and use it to generate whole stacks of needles.

The most striking advances may be in medicine. PCR has enabled doctors to speed the diagnosis of some hereditary diseases and has led to the discovery of new mutations that have caused such disorders.

Determining Spread of Infection

The technique is beginning to play a major role in the study of AIDS, permitting scientists to detect viruses that may be hiding in as few as one in a million of a patient's white blood cells. Experts predict that PCR tests will increasingly be used to determine, with much greater precision than in the past, whether people are infected with the AIDS virus and how the infection progresses inside the body.

"It is having a revolutionary impact," said Dr. Haig H. Kazazian of Johns Hopkins Medical Institutions, who has used the new technique to increase speed and accuracy in diagnosing cases of sickle cell anemia and beta thalassemia, hereditary disorders of the red blood cells.

Unlike many advances in modern biology, which are made by scientists at universities and then put to commercial use by biotechnology companies, PCR was developed directly by a company — the Cetus Corporation of Emeryville, Calif. It is now coming into wide use for both academic research and commercial purposes.

The idea was originated by Dr. Kary Mullis at Cetus about four years ago and was developed into its present form by a team of scientists at the company, said Dr. Henry R. Erlich, director of human genetics at Cetus. Last November, the company, in collaboration with the Perkin-Elmer Corporation, announced development of a kit of equipment and materials for automated use of the new technique.

"Fairly quickly it was apparent that it was a very important development," Dr. John Gibbs of Baylor College of Medicine in Houston said of the technique. "But we have continually been surprised at how important it has become."

The ability to multiply small bits of genetic material was crucial to the studies of the ancient brain because, after 7,000 years, only traces of genetic material remained, and much of it was damaged and contaminated by bacteria. With conventional techniques alone, it would have been questionable whether any useful DNA could have been grown from tissue samples.

Link With Antiquity

The use of the new technique made a great difference, said Dr. Svante Paabo of the University of California, Berkeley. In 1985, he used older methods to grow a small amount of DNA from an Egyptian mummy estimated to be 2,400 years old. The new technique that Dr. Paabo and his colleagues used with the brain tissues from Florida made it possible to copy and reproduce in large quantity some of the few pieces of DNA that were still intact.

The research is still in progress, a collaboration between the University of California and Dr. John A. Gifford of the department of anthropology, University of Miami. It is not yet clear how much the studies will reveal about these early human inhabitants of the Western Hemisphere, but the DNA samples are certainly the first direct clues to their heredity.

The research group at the University of California, led by Dr. Allan C. Wilson, has also grown DNA from a woolly mammoth that lived 40,000 years ago in Siberia, finding chemical evidence, as expected, that the animals were related to the ancestors of modern elephants. Dr. Wilson believes the new technique will prove to be a valuable tool in studying the evolution of many species, including humans, with a precision never before possible.

In presentations at the international conference on AIDS last week in Stockholm and in earlier reports, scientists described

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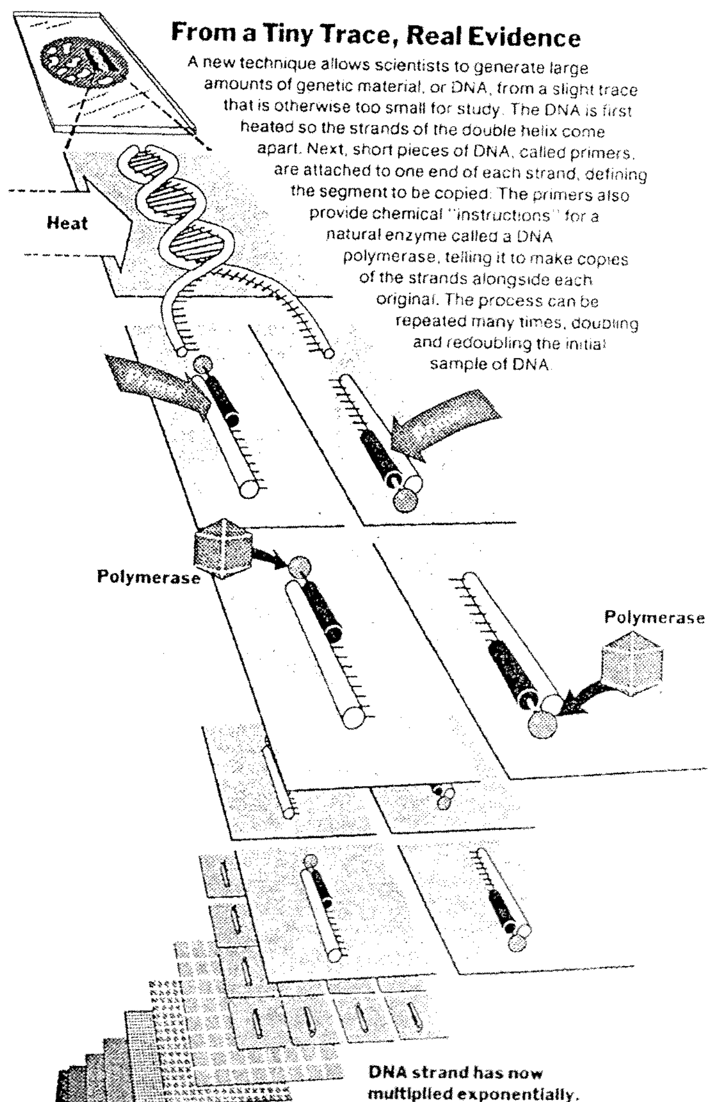

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their use of the PCR technique to prove that viruses can lurk for years in certain cells, undetectable by conventional tests and sometimes without stimulating production of the antibodies that are the evidence sought by the most commonly used tests for the AIDS virus.

Experts said the PCR test will allow earlier detection of infection with the AIDS virus and, by making it easier to find the virus, may improve the understanding of the course of the disease. Some research centers are already using PCR for study of acquired immune deficiency syndrome, and some laboratories are using PCR through license by Cetus.

Tests in Infants

One report in Stockholm, from scientists of the Cetus Corporation and Northwestern University, showed that it was possible to identify infants who were born infected with the AIDS virus many months earlier than had previously been possible. By using this technique to test babies of mothers known to be carriers of the virus, doctors will be able to determine quickly whether an infant needs special medical care and, as they are developed, anti-AIDS treatments.

Dr. Gibbs of Baylor has used the technique to improve diagnosis of two important genetic diseases, Lesch-Nyhan disease, which affects the central nervous system, and Duchenne muscular dystrophy, a wasting disorder of muscle. His group has found nine specific mutations — gene defects — that have never before been seen in these two diseases.

Similarly, Dr. Kazazian's group has found several new mutations in the

It enables scientists to study extremely small traces of genetic material.

gene that causes beta thalassemia when defective, bringing the total of such defects to more than 50, all affecting the same gene in slightly different ways. At both laboratories the mutations were found by close analysis of portions of the patients' DNA that had been grown in large quantity by the PCR technique.

The use of PCR in searching for evidence of a hidden virus is illustrated by the example of the AIDS virus. First, using a probe technique already available, scientists extract from blood cells bits of genetic material that may be, but are not certainly, from the AIDS virus. This step is possible because the chemical structure of the genetic material of the AIDS virus is already known. A small piece of known DNA that matches a particular piece of the virus's genetic material is used as a probe to find any matching piece of DNA in the vast tangle of strands of cellular DNA that would be found in any laboratory specimen of cells. The probe attaches to the matching piece.

But to determine that the matching piece of DNA is actually from the AIDS virus, larger amounts must be produced for study. By conventional methods that can be a cumbersome process that may take weeks.

The PCR technique, though, produces the larger amounts in days or even hours.

The first step is to heat the DNA so that the two strands that make up the double helix come apart.

Next, short pieces of DNA called primers are attached to one end of each strand of the sample so that the two flank the segment that is to be copied. These primer pieces define the portion of DNA to be copied and also provide chemical "instructions" for the third and final step in the procedure.

This third step is to add an enzyme called a DNA polymerase, a natural substance that copies a piece of DNA when it finds the proper instruction signals on the strand it encounters. At this point, the enzyme does just what it does in nature: it assembles a second matching strand of DNA along each original so that a new double helix of DNA is produced, with all of its subunits matching perfectly.

The three-step process doubles the amount of DNA that was in the original sample, including the primers.

Thereafter, each repetition of the three steps doubles the amount of DNA from the last sequence. In this geometric progression, 20 repetitions will copy the original DNA sample a million times.

In a few hours, this can produce as much DNA as conventional methods produce in weeks. Furthermore, it can generate copies from samples that would often be too small to be reproduced and identified by conventional means.

When the technique was first developed, it was necessary to put in a fresh supply of the polymerase enzyme for each new three-step sequence. Recently, designers of the system have used a polymerase from bacteria that live in hot springs. They are sufficiently heat-resistant to survive the near-boiling temperature needed to separate the DNA strands and can be used over and over again as the chain reaction is repeated.

In crime-solving work, PCR has made it possible to analyze the less than 10 billionths of a gram of DNA that can usually be recovered from a single human hair. Conventional means of analysis would require a thousand times as much. Human hairs are among the most common items of biological evidence to be found at the scene of a crime, but it is usually impossible to pin down the source of any single human hair.

Only One Body

Dr. Erlich said the new technique was used in one recent case to dispose of the suspicion that small autopsy samples from two different people had been switched to confuse the prosecution in a murder case. The PCR studies showed that the samples had not been exchanged. They came from the same person.

Experts at Cetus got into the forensic uses of the technique through earlier studies in which human tissue types were being studied to gauge individuals' susceptibility to certain diseases, such as insulin dependent diabetes and rheumatoid arthritis.

It has been known for years that people who are at relatively high risk of developing such diseases and a broad range of less common autoimmune disorders can be distinguished by immunological typing of tissues involving what is known as the HLA system. Similar typing using variations in DNA made detectable by the PCR method can achieve far greater refinement of human tissue types than conventional HLA typing, Dr. Erlich said.

The University of Miami/John Gifford

A 7,000-year-old brain found in Florida. A new technique of multiplying genetic material may shed light on the heredity of ancient Americans.

HLA typing produces profiles so detailed that they can often be used to identify possible fathers in cases of disputed paternity. The same kind of genetic fingerprinting has proved useful in some criminal cases.

The new technique is proving useful in a broad range of studies involving virus infections and the actions of particular genes that have normal functions but seem to be involved in the cancer process under some circumstances, the so-called oncogenes.

A few weeks ago, medical scientists of the State University of New York in Brooklyn and Syracuse and specialists in PCR work at Cetus reported studies that link a known human cancer virus, HTLV-1, to a progressive type of paralysis called chronic progressive myelopathy. They found the link with the help of PCR. Some scientists think the technique will also prove useful in discovering viruses that may play roles in other nervous system disorders, possibly including multiple sclerosis.

Much of the forefront of biological research today is involved with studies of genes and their actions in both health and disease and genes are pieces of DNA.

"It seems to have applications in every facet of DNA work," Dr. Gibbs of Baylor said of the technique.