

Treasure hunt unearths cholesterol gene

A small land mass rising out of the Chesapeake Bay, Tangier Island served as a base for British troops during the Revolutionary War and the War of 1812. Pirates, too, found this sandy isle a safe haven.

Forty years ago, Tangier Island became home to a medical mystery as physicians puzzled over an island boy who had orange tonsils. Scientists have now solved this mystery, and in doing so, they have raised hopes of thwarting the buildup of artery-clogging cholesterol that can lead to heart disease.

The boy with oddly colored tonsils had a rare genetic disorder, now known as Tangier disease. The condition's defining feature is a paucity of high-density lipoprotein (HDL), the so-called good cholesterol.

Normally, each HDL particle, whose core includes several proteins and a bit of cholesterol, picks up additional cholesterol from cells and transports it to the liver for clearance. In Tangier disease, an inability to eliminate the yellow cholesterol from cells in the tonsils, due to a lack of HDL, accounts for their orange hue. The illness can have more serious consequences. The abnormal accumulation of cholesterol promotes atherosclerosis and kills nerve cells throughout the body.

People with Tangier disease—there are only few dozen known cases in the world—do form the HDL cores. Their cells, however, do not transfer cholesterol onto the cores, and their bodies rapidly destroy the immature particles.

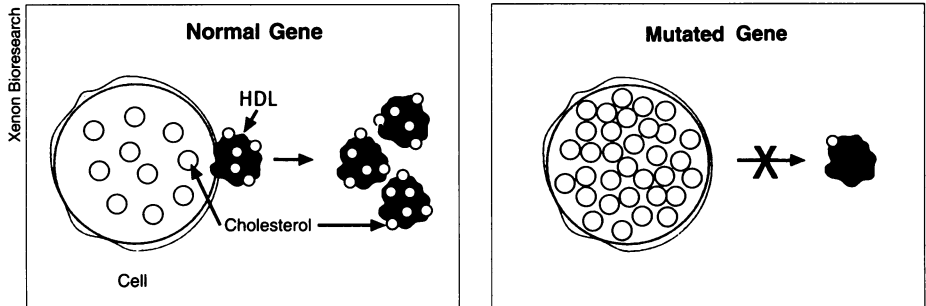
In the August *NATURE GENETICS*, groups led by Michael R. Hayden of the University of British Columbia in Vancouver, Gerd Schmitz of the University of Regensburg in Germany, and Gerd Assmann of the Westfälische Wilhelms University in Münster, Germany, independently report the discovery of a gene in which mutations cause Tangier disease. The groups found that people with the condition have two flawed copies of the gene. In several families with a less-severe HDL deficiency, whose origin was believed to be distinct from Tangier disease, Hayden's team found that affected members have a single defective copy of the gene.

The gene encodes a protein whose structure strongly hints that it transports cholesterol across cell membranes. When a mutation makes this transporter defective or prevents its production, cholesterol apparently remains inside a cell.

Scientists are now rushing to see if more-subtle alterations in the transporter gene also alter the protein's function and predispose people to heart disease. "There are a lot of people who have low levels of HDLs and have an increased risk of coronary artery disease. Is this transporter abnormal not only in Tangier disease, but in these other patients?" asks

H. Bryan Brewer Jr. of the National Heart, Lung, and Blood Institute in Bethesda, Md.

The discovery of this presumed cholesterol transporter suggests methods to prevent harmful cholesterol buildup. While there are drugs to reduce concentrations of a person's low-density lipoprotein, the so-called bad cholesterol, doctors have nothing with which to raise HDL concentrations.



In normal cells (left), a protein removes cholesterol, placing it on HDL particles. In Tangier disease (right), this transporter fails and cholesterol builds up in cells.

Antibodies may treat overdoses, addiction

People receive routine immunizations to produce antibodies that stave off infectious diseases such as measles and the flu. Now, researchers have created a vaccine and antibodies that they expect to combat the harmful effects of addictive drugs.

At the American Chemical Society meeting this week in New Orleans, researchers described antibodies created to block the effects of cocaine and the hallucinogen PCP, also known as angel dust. In the blood, these antibodies would "soak up [the drugs] like sponges," says Kim D. Janda of the Scripps Research Institute in La Jolla, Calif., and prevent cocaine or PCP from reaching the brain.

Tested only in rats so far, the new treatments are intended to treat drug overdoses and help patients overcome addiction (*SN*: 12/16/95, p. 406). Janda's team plans to administer a potential vaccine to people in tests beginning in a few months.

Because it's small, the cocaine molecule normally evades the immune system. Janda and his colleagues attached cocaine molecules to a large protein that the immune system recognizes as foreign. The researchers injected these compounds into rats, which then produced antibodies against cocaine and prevented relapses in the animal model of addiction. Next, the team will test whether proteins linked to cocaine can induce the same response in people.

In a second approach, the researchers have harvested anticocaine antibodies from rats and then genetically engineered the antibodies to make them more tolera-

The transporter "provides us with a unique opportunity to develop agents to help people who have early heart disease," says Brewer. "We may be able to find drugs and other ways to regulate [the transporter] and remove excess cholesterol from the cell."

One option is gene therapy. Margaret E. Brousseau of Tufts University in Boston says that physicians could add copies of the transporter gene to macrophages, the cholesterol-laden cells that may initiate arterial blockages. —J. Travis

ble for people. The team then produced large quantities of the modified antibodies in laboratory bacteria.

Using a similar approach, S. Michael Owens of the University of Arkansas for Medical Sciences in Little Rock and his colleagues have created antibodies against PCP, a drug that produces violent, schizophrenic behavior. A single dose of the antibody reduces the psychoactive effects of PCP in rats for at least 2 weeks, equivalent to about 1 to 2 months in people, says Owens.

Antibody therapy could help patients kick a PCP habit, says Frank Vocci of the Medications Development Division at the National Institute on Drug Abuse in Bethesda, Md. "A person who is drug dependent has a high relapse potential by taking just a small amount of drug," he says. Antibodies that block the drug's action could reduce this danger.

For emergency treatment of life-threatening overdoses, Owens and his group have also created antibody fragments that inactivate PCP. Unlike whole antibodies, the fragments with the bound PCP are cleared from the body within a day or two. Vocci says, "Having an antibody to pull the drug out of the tissues would be potentially beneficial."

Vaccines and antibody therapy alone won't cure someone of drug addiction, the researchers emphasize. Doctors would have to administer such medication as part of a behavior-modification program, says Owens. "The person makes a commitment to quit, and we give them a crutch in case they mess up," he explains. —C. Wu