What's That Smell?

Modern science puts its mark on a rare but ancient body-odor disease

By DAMARIS CHRISTENSEN

"What have we here? A man or a fish? Dead or alive? He smells like a fish; a very ancient and fish-like smell . . ."
—William Shakespeare, "The Tempest"

Shakespeare's description of the socially rejected island dweller, Caliban, aptly demonstrates that people have long been aware of a particularly offensive smell. Today, body odors are among the most sensitive of topics and figure into some of the deadliest insults.

Inspired by advertising, most people avoid having a socially unacceptable smell thanks to frequent showers and deodorants, perfumes, or colognes. However, for people with a rare genetic disorder known as fish odor syndrome, none of these is enough.

Since few health professionals are aware of this disease, also called trimethylaminuria, people experiencing its characteristic body odor may spend years seeking relief. They often acquire a long list of inaccurate diagnoses, ranging from poor hygiene to psychiatric problems. These people may withdraw from the outside world to avoid ridicule or try to mask their odor with strong perfumes and cigarettes. Many of those with the disorder also report symptoms of depression.

"People think this disease is a laughing matter, but for the people who have it, it is not. This syndrome can be highly destructive to a person's personal and social life and to their work and career," says Robert L. Smith, a molecular toxicologist at the Imperial College School of Medicine in London who recently cochaired the first-ever scientific meeting on trimethylaminuria. Held in late March at the National Institutes of Health in Bethesda, Md., the conference gathered from around the globe about 30 researchers studying trimethylaminuria—many of them without funding—and a few of the people who have been diagnosed with the disorder.

The first case of trimethylaminuria was described in the medical literature in the 1970s, but literary references may go back a thousand years. For example, an ancient Hindu tale describes a maiden who "grew to be comely and fair, but a fishy odor ever clung to her."

Although they show no apparent lack of hygiene or obvious medical symptoms, most people with the disorder report having foul body odors, bad breath, or a bad taste in their mouths. Studies in the last few years have shown that trimethylaminuria results from defects in an enzyme that breaks down trimethylamine, a byproduct of protein digestion released by bacteria living in the gut. This small molecule—the compound that gives fish their fishy odor—smells foul or garbagelike at low concentrations and fishy in larger amounts.

People with the disorder can release trimethylamine through breath, sweat, and urine. A few have a strong odor all the time, but most others experience a less severe smell that fluctuates over time. Researchers speculate that the variability of symptoms indicates that a range of genetic mutations can cause the disease and that stress and diet play a role in triggering symptoms.

There is no cure for fish odor syndrome, but a special diet can alleviate the worst of the odor problems. This low-protein regime restricts the amino acid choline, a building block of protein naturally found in high concentrations in fish, eggs, beans, and organ meats. Some people also report that limiting lecithin, a common food additive that is also naturally found in eggs, soybeans, and corn, helps reduce odor.

Because bacteria in the gut produce most of the trimethylamine in the body, some people have found that low doses of antibiotics, which kill off these bacteria, temporarily help keep odor down.

Although only about a hundred cases have been described in the scientific literature worldwide, the syndrome may not be as rare as that number suggests. Estimates of the disease's prevalence are sketchy at best.

Odor problems are such a sensitive topic that many people may be wary of talking about their symptoms to a doctor, says Harry W. McConnell of King's College Hospital in London. "The name [fish odor syndrome] contributes greatly to the stigma of this disorder," he says, adding that the name "is misleading since the odor is variable."

Because the disease is practically unknown by any name, it may take years for a person with trimethylaminuria to find a doctor who can recognize the problem. In a survey given to 22 people who had been identified as having the syndrome, McConnell found that it typically took them 5 to 10 years to seek medical care after their symptoms appeared. The correct diagnosis then required, on average, another 10 years.

Trimethylaminuria is only occasionally identified during childhood. The affected children, however, are likely to become disturbed and even suicidal because of the problems their odor causes in schools, says Ertan Mayatepek of the University Children's Hospital in Heidelberg, Germany. The odor problems in some children seem to disappear as they age, but researchers don't know why.

Nor do they know why the syndrome seems to be more common in women than in men. Scientists suspect that sex hormones exacerbate symptoms. A variety of reports say that the disease in women gets worse around puberty, just before and during menstrual periods, after taking oral contraceptives, and around menopause.

Finally, some cases of trimethylaminuria may have no genetic component: Several patients seem to have developed the disorder after liver or kidney disease.

Scientists discovered the gene implicated in trimethylaminuria in 1997. Located on the end of a chromosome, it encodes one of a series of enzymes called flavin monooxygenases (FMOs). Researchers suspect that these enzymes' most important role is in eliminating environmental toxins from the body. The enzyme known as FMO3, for example, helps break down diet-derived nitrogen-containing compounds, including trimethylamine, and possibly drugs containing nitrogen, sulfur, and phosphorus.

The gene for FMO3 can suffer from any of about 10 different mutations. Most people showing symptoms of trimethylaminuria have inherited two mutated copies of

the gene. Scientists suggest that the variety of genetic mutations might explain differences in the timing of disease onset and how strong the odor is.

Environmental factors may also play a role. Some types of bacteria that people have in their guts might produce more trimethylaminuria than other types, speculates Paul V. Fennessey, a pharmacologist at the University of Colorado Health Sciences Center in Denver. Alternatively, if the enzyme that breaks down trimethylaminuria is just barely keeping up, sudden increases in the amount of trimethylamine eaten or produced in the body could trigger symptoms, he adds.

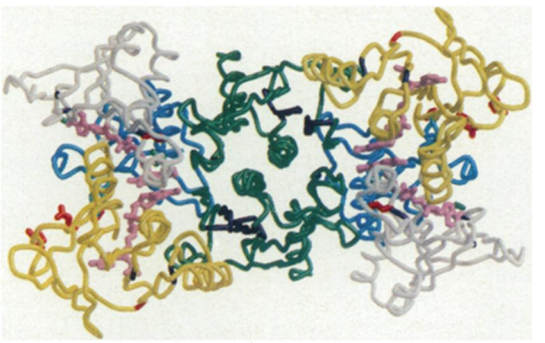
Animal studies have provided evidence that a compound known as indole-3-carbinol, found in broccoli and other dark green vegetables, blocks the function of the enzyme system that breaks down trimethylamine, says David E. Williams, a molecular toxicologist at Oregon State University in Corvallis. If this holds true in people, avoiding broccoli and other leafy greens, in addition to limiting protein intake, might help reduce odor problems, he says.

Some studies have suggested that people who carry only one copy of a mutated gene may be susceptible to transient fish-odor attacks during periods of stress or after eating foods that contain large amounts of trimethylamine or its chemical precursors, says Stephen C. Mitchell of the Imperial College School of Medicine. Doctors can use this observation to identify carriers of the mutated gene. When they receive a high dose of choline, people with at least one copy of a mutated gene for FMO3 excrete high levels of smelly trimethylamine in their urine. This test is also used to diagnose trimethylaminuria.

Because FMO3's functions in the body are not well understood, doctors don't know what symptoms, other than odor, might be linked to trimethylaminuria. Researchers suspect that the enzyme breaks down many substances besides trimethylamine. For example, various drugs, such as antidepressants, may be broken down by FMO3. If the enzyme isn't working properly, people might suffer additional side effects from some of these drugs, they suggest. A few people with trimethylaminuria at the conference reported that they had taken antidepressants, but the drugs did not seem effective and actually worsened their odor.

Animal studies also support the idea that FMOs break down drugs. Indole-3-carbinole, which inhibits FMO3 and its relatives, seems to increase the effectiveness in mice of the pain medication codeine, Williams reports. These findings suggest that the drug is broken down differently when the FMO system is not working, he says. Test-tube experiments in his laboratory suggest that the enzyme system may also help break down nicotine and the anticancer drug tamoxifen.

The liver, a reservoir of digestive enzymes, produces most of the body's FMOs. Production of these proteins has also been detected in midbrain nerve cells, skeletal muscle, adrenal and salivary glands, thyroid and lung tissue, and the skin. The functions of the enzymes in these various locations remain unknown.



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In this model proposed for the enzyme flavin monoxygenase 3 (FMO3), red designates mutations known to alter the enzyme's function, some of which cause trimethylaminuria. White, yellow, green, and blue indicate structurally different areas of the enzyme, and purple represents compounds required for the enzyme's action. A different group of researchers developed the structure for FMO3 on the cover of this issue.

Although the vast majority of people so far diagnosed with the disorder appear to have normal mental and physical abilities, some researchers suspect that the enzyme deficiency itself may cause depression and trigger seizures. For example, a Pennsylvania teenager with trimethylaminuria and a tendency to suffer seizures found that his seizures stopped when he went on a protein-restricted diet, says McConnell.

The unanswered questions about trimethylaminuria seem endless, yet money to support studies of the disease is scarce, say researchers. Because the Wellcome Trust in England has sponsored several studies of the disease, Britain has the dubious distinction of having the most reported cases of fish odor syndrome in the world.

At the recent NIH conference, researchers called for development of a new diagnostic test that will be less off-putting—the current assessment procedure temporarily makes the symptoms worse. The researchers also saw a need for a consortium that would coordinate clinical research so that studies could include more than a few participants. The meeting organizers hope that patients will form an advocacy group to raise money for research into this rare disease.

"There are two very difficult aspects of this disorder," McConnell says. "One is diagnosing it in the first place. The second is treating it, since it isn't enough to just give people a list of things they can't eat, which includes most of their previous diet." Moreover, the people with the syndrome complain that it's difficult to find out which foods contain choline and lecithin.

Doctors don't expect antibiotics to become the treatment of choice because they aren't effective enough to control the disease without a restricted diet. Even if they were more effective, regular use of antibiotics would upset the digestive system and raise the specter of life-threatening drug-resistant infections.

If mutations in the FMO3 gene are as common as scientists suspect, it might be worth developing a screening test to be used at birth, says Eileen Treacy of the Montreal Children's Hospital.

Challenge tests for trimethylaminuria in England indicate that up to 1 percent of people worldwide carry at least one copy of a mutated gene for the critical enzyme, McConnell reports. Because people must inherit two copies of a mutated gene to show symptoms of the disease, 1 in 10,000 people would be expected to have the syndrome. Researchers believe that equatorial regions have even higher percentages of people carrying the mutated genes, McConnell says.

Treacy points to the metabolic disorder known as phenylketonuria, or PKU. The disease causes mental retardation and nervous system problems in about 1 child in 12,000. Because PKU can be treated successfully with diet and drugs, every child born in a U.S. hospital is screened for the disease. Trimethylaminuria and PKU probably affect roughly similar numbers of children, meaning screening for trimethylaminuria is a realistic possibility, she says.

The ignorance and confusion surrounding trimethylaminuria are perhaps the most devastating parts of the disease, says McConnell. "It's absolutely essential to get the word out. We have a potentially treatable disorder that is grossly underdiagnosed," he insists.

Sandy Gordon, a New Yorker, quit working because of her odor. Before discovering that she had trimethylaminuria, she spent almost $30,000 on tests and five exploratory surgeries that her health insurance wouldn't pay for.

"At this point, I don't want a cure. I just want information," says Gordon, who has started an informal support group for people with trimethylaminuria. "I just want people with this disorder to know they are not crazy." □