Sphinx of Fats

Some lipids, wallflowers for a century, show therapeutic promise

By JANET RALOFF

Nine years ago, isolated horse owners from Arizona to Pennsylvania confronted a similar nightmare. It started when some of their animals acquired a strange gait. Before long, the animals' movements became alarmingly uncoordinated, tremors set in, and the horses went blind. In less than a month, they were dead.

Autopsies revealed that the animals had suffered a "brain meltdown," recalls Ronald T. Riley of the U.S. Department of Agriculture's Agricultural Research Service in Athens, Ga. Frank Ross of USDA's Animal and Plant Health Inspection Service in Ames, Iowa, offers a more specific description: "liquefaction of the white matter of the brain."

The horses had succumbed to moldy corn disease, also known as leucoencephalomalacia. Though this equine scourge has surfaced now and again for years—usually on an isolated farm or two—it mushroomed into an epidemic briefly during the late 1980s.

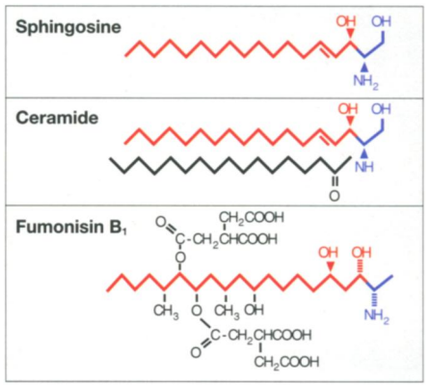
Around the same time, researchers in South Africa showed that if a fungal toxin present in nearly all corn was eaten in very high amounts, it could trigger esophageal cancer in humans. This same toxin, fumonisin B_1, was suspected of causing the equine disease—a conjecture eventually confirmed experimentally by Ross and others.

In the wake of the equine epidemic, Riley began investigating the toxicology of this fumonisin. He never suspected that the studies would almost immediately begin paying off with answers to a far broader, century-old conundrum: the function of a class of arcane, though ubiquitous, fats.

At the start of this investigation, observes Alfred H. Merrill Jr., a biochemist at Emory University in Atlanta, the significance of these complex fats—called sphingolipids—was obscure (see sidebar). The past decade, however, has seen the emergence of a cornucopia of clues, hinting at a wide variety of roles for them.

Though their precise functions have yet to be fully characterized, sphingolipids "appear essential" and intimately involved in the healthy functioning of all cells, notes oncologist Yusuf A. Hannun of Duke University Medical Center in Durham, N.C. Indeed, he now believes that by tinkering with their production—or enriching bodily concentrations of them through diet—physicians may help prevent or treat a host of diseases, including cancer.

Ironically, since their discovery a century ago, sphingolipids have been associated primarily with causing rather than preventing disease. About a dozen rare, catastrophic inherited disorders—including Gaucher's, Tay-Sachs, Fabry's, and Sandhoff diseases—stem from defects in genes that control the production of one or another of the enzymes that break down sphingolipids. The resulting buildup of the affected fat can prove fatal.



The most basic sphingolipid is sphingosine (top), made from the fatty acid called palmitic acid (red) and the amino acid serine (blue). The body fashions more complicated members of this extensive family of fats by tacking additional fatty acids—as seen in ceramide (center)—and sometimes sugars onto this sphingosine backbone. The toxin fumonisin B_1 contains a similar backbone, plus several chemical groups.

"When I was in medical school," notes James A. Shayman of the University of Michigan in Ann Arbor, "I'd be lectured on these diseases for a day or two—and then forget about them. Because up until about 10 years ago, there was pretty limited information about the normal role of these [fats]." However, he says, "the complexity of these lipids, which is quite profound, suggested that they must play a number of roles in normal cell biology."

One of the first clues emerged in 1986, when Hannun, Merrill, and their colleagues discovered that sphingosine, the simplest fat in this family, is a potent inhibitor of protein kinase C (PKC). This enzyme plays an important role in various activities, including cell growth, blood clotting, hormone action, and even learning (SN: 5/25/91, p. 328).

After the equine epidemic of moldy corn disease, Riley observed that fumonisin B_1 closely resembles several sphingolipids, including sphingosine. He and Merrill tested the toxin to see if it also affected PKC. To their surprise, it did not, but it dampened the exposed cells' natural production of sphingolipids.

"That was exciting," Riley recalls. Not only did their finding suggest that fumonisin might trigger the horse disease and human cancer through a sphingolipid deficiency, it also offered some of the first solid, if indirect, support for the idea that normal concentrations of these fats might be essential to health.

Most of us think of fats as compounds that the body burns to get energy or that it stores in depots that eventually swell the waistline. In addition, however, fats can be either broken up or combined with other compounds to form new entities with more specific roles. In many cases, the new compound relays messages between cells or even within a cell.

A growing number of research teams has begun turning up evidence that sphingolipids are among the fats that function in this way. Fumonisin has proved a key tool for teasing out these roles, Riley notes.

The toxin allows molecular biologists to knock out a sphingolipid in some cells in test tubes, then observe how this changes the cells' growth, biochemistry, and responses to outside stimuli.

The studies have already uncovered at least 10 distinct sphingolipid roles—many of them fairly basic and mechanical. The fats guide and stabilize the branching of certain brain neurons, regulate cell cycling, and help cells differentiate. A major challenge, according to Riley and Merrill, will be to find the molecular switch that stimulates a sphin-

golipid into promoting or slowing cell growth or killing cells outright.

Ceramide, one of the basic sphingolipids, may be such a switch, Hannun believes, or at least be central to what he terms a "lipid biostat." In the Dec. 13, 1996 SCIENCE, he theorized that such a system would "measure and initiate responses to cellular stress, much as a thermostat measures and regulates temperature."

Cells often have a fairly general response to stress, whether in the form of heat, radiation, chemical poisoning, or internal agents that signal the presence of external threats. In most cases, Hannun says, cells respond to extreme stress by undergoing programmed cell death or by shutting down their normal replication cycle so the body can repair any damage.

Experiments by his group and others, he notes, now "suggest a role for ceramide in various forms of [cell] growth suppression and cell death"—perhaps through its ability to serve as a stress sensor.

Many cellular enzymes, each sensitive to different stressors, or signaling molecules, can turn on ceramide production. Hannun now suspects that a cell's total ceramide concentration may "serve as a gauge of the overall amount of stress or injury to which the cell has been exposed."

How the warned cell then responds may depend on further interpretation of the threat by enzymes, biochemical switches, and other systems operating downstream of the ceramide signal.

Ceramide's apparent signaling of stress represents just one of the growing number of health-promoting roles associated with sphingolipids. For instance, Hannun says, these fats can also initiate the programmed death of abnormal cells and can trigger the transformation of undifferentiated cells, as in cancer, into more normal ones.

Taken together, he says, these findings suggest that by overcoming deficiencies in sphingolipids or by meeting the increased need for them as disease develops, a cancer's growth might be slowed or arrested.

Merrill's latest studies lend some support to that suspicion. In the Nov. 1, 1996 CANCER RESEARCH, for instance, his team analyzed the therapeutic potential of sphingolipids on the development of cancer in mice. They injected the animals with a chemical known to induce colon cancer, then fed them either a normal diet or one enriched with sphingomyelin for 34 weeks.

"We found no reduction in the overall number of tumors that animals in the treated group developed," he notes. However, "what did excite us was a difference in the nature of the tumors." Nearly one-third of those in the sphingolipid-treated animals were benign—essentially precancerous. In contrast, every tumor in the untreated animals had become an invasive cancer.

Cancer isn't the only disease that may prove amenable to sphingolipid therapy. Shayman is exploring whether limiting the availability of a sphingolipid can curb the kidney damage frequently associated with diabetes.

Within 2 months of the onset of diabetes, the kidneys double in weight. As concentrations of sugar in the blood climb during the early stages of the disease, so does the kidney's production of a sphingolipid made from the coupling of a sugar molecule to ceramide. Working with rats, Shayman has found that by blocking the formation of these sphingolipids, "you can reverse the [kidney] growth"—and, presumably, the more dramatic damage that usually follows.

"So we're now faced with the possibility that diabetic [kidney damage] is sphingolipid-mediated," he says—and treatable. In the United States, he points out, diabetes underlies most cases of kidney failure.

Finally, new therapies are being explored to treat those classic genetic disorders caused by excessive buildups of sphingolipids. For instance, an international team of scientists has just reported successfully using a drug to treat mice that were genetically predisposed to build up unhealthy concentrations of ganglioside in the brain. An inability to break down this sphingolipid produces Tay-Sachs disease in humans.

The drug works by reducing the body's production of the material from which ganglioside is made.

Writing in the April 18 SCIENCE, Frances M. Platt of the University of Oxford in England and her colleagues conclude that "theoretically, this therapeutic strategy could be applied to all of these [sphingolipid-storage] disease states," regardless of which fat the body has trouble breaking down.

In fact, many pharmaceutical companies are already hard at work developing therapeutic products based on sphingolipids. Most of these ventures are still in their early stages, so one shouldn't expect to see new drugs flooding the market in the next few years, notes Robert M. Bell, a vice president for research at Glaxo-Wellcome in Research Triangle Park, N.C., and a pivotal player in identifying sphingolipids' cell-signaling role.

Merrill is pleased that, after nearly a century of relative stagnation, sphingolipid research is at last taking off. However, as a former JOURNAL OF NUTRITION editor, he wishes that scientists who study the potential pharmacological properties of foods would take more notice of these fats. To date, he says, because these researchers have largely ignored sphingolipids, "they haven't begun to address whether their presence in food might be related to any beneficial effects of diet on disease prevention."

He also laments the paucity of data on which foods contain ample stocks of these fats. It's a subject his lab has begun to probe. Among the richest dietary sources of sphingolipids identified so far are soy and cow's milk. These fats do not separate with the cream during milk processing. Indeed, the sphingofat served to mice in his colon cancer study came from nonfat dried milk. "Which," Merrill muses, "should probably change our way of thinking about 'nonfat' milk." □

A sphingo what?

Most people are familiar with the lipids, or fats, that lace our diets. These include monounsaturates like oleic acid, polyunsaturates such as linoleic acid, and saturated fats such as palmitic acid.

Until fairly recently, however, even most lipid specialists would have raised a puzzled eyebrow at the mention of sphingolipids. For years, Alfred H. Merrill Jr. of Emory University in Atlanta attended scientific meetings wearing a button that read, "Ask me about sphingolipids." Hardly anyone did.

Johann L.W. Thudichum encountered much the same apathy when he tried to discuss these chemicals during the latter half of the 19th century.

A German surgeon-chemist who worked in London, Thudichum delighted in probing the function of various natural constituents of the brain, especially one particular fatty material. A rival chemist had named it protagon, to signify that it constituted the most important building block of the brain. Thudichum's work, however, suggested that protagon was itself made of two more elemental units. Around 1874, he published the exact chemical composition of these smaller building blocks. To denote their enigmatic, Sphinxlike nature, Thudichum termed them sphingolipids.

The name proved apt. Despite intense scrutiny, their biological function eluded him, as it did most scientists until about a decade ago.

One reason sphingolipids remained such a quiet area of research for so long, notes Ronald T. Riley of the USDA in Athens, Ga., is that their initial isolation from brain tissue gave many scientists the mistaken impression that they occur nowhere else. In fact, they appear in every cell of the body. However, "they were also so hard to work with that nearly everybody stayed away from them"—until a few enigmatic diseases and poisoning incidents opened a back-door approach to understanding them. —*J. Raloff*