

Emeritus: On the trail of aflatoxin

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Photo: Calvin Campbell

In the spring of 1960, a mysterious liver disease killed hundreds of thousands of turkeys in the United Kingdom. The outbreak was soon traced to ground peanut meal, shipped from Brazil and contaminated with mold that produces a poison known as aflatoxin.

At the time, little was known about [aflatoxin](#), but some scientists suspected it could be linked to liver cancer in humans. Soon after the U.K. [outbreak](#), a young MIT toxicologist named Gerald Wogan launched a thorough, decades-long investigation into the toxin, eventually exposing it as one of the most potent carcinogens humans can encounter.

Throughout his career, Wogan not only made discoveries illuminating aflatoxin's role in liver cancer, which kills about 600,000 people a year, but he also used his knowledge to shape food-safety regulations in the

United States and Europe, and helped develop new measures that could fight liver cancer in developing countries, where aflatoxin exposure is still common.

“A lot of people are content to do basic science, but he picked up that mantle of responsibility and went right into the regulatory arena,” says John Essigmann, MIT professor of toxicology and chemistry and a former student of Wogan’s.

A new toxin

Though he has become one of the world’s foremost experts in toxicology, Wogan started his career as a physiologist. He came to MIT in the summer of 1961 to join a new program in food safety, which was part of the Department of Nutrition, Food Science and Technology.

At the time, food safety was a hot topic. “It was right after Rachel Carson published *Silent Spring*, and there was a lot of concern about pesticide residues and chemical residues and contaminants,” recalls Wogan, who turned 80 this summer.

Upon arrival at MIT, he planned to study a puzzling toxic agent known as chick edema factor (later shown to be dioxin), which causes the sack around the heart to fill with fluid. However, shortly after the [liver-disease](#) outbreak in British turkeys, a UNICEF scientist urged him to look into the pressing problem of aflatoxin.

By then, British scientists had isolated and named the poison, but hadn’t determined its chemical structure or figured out why it was so toxic. In 1962, Wogan attended a conference on aflatoxin in London, where a British pathologist offered him a sample of the fungus. Wogan slipped two Petri dishes containing the fungal colonies into his coat pocket and carried them onto the plane and across the Atlantic, back to MIT.

When Wogan got the fungus (known as *Aspergillus flavus*) back to his lab, “we started growing the mold on everything we could think of” — not just peanuts, but also wheat, corn and rice. Wogan and George Buchi, a natural-products chemist in MIT’s Department of Chemistry, became the first to figure out aflatoxin’s structure and synthesize the two major forms of aflatoxin, in 1963 — just beating out a European team that was racing the MIT group to the structure.

Human health

Wogan and veterinary pathologist Paul Newberne then started measuring aflatoxin’s effects in rats. Wogan used those results to persuade the FDA to establish guidelines, still in use, for the maximum allowable amount of aflatoxin in foods such as peanut butter.

“From the beginning, the goal was not only to understand the mechanisms of action and try to characterize it as completely as we could, but to try to understand what impact it had on human health,” says Wogan. “The only reason I was interested in aflatoxin is because it was clear there was a large potential human risk.”

To strengthen the link between aflatoxin and liver cancer in humans, Wogan set up an epidemiological study in Thailand in the late 1960s. Researchers from MIT and Thailand, in a collaboration dubbed MITHAI, measured aflatoxin levels in people’s food and compared them with their liver-cancer rates.

After collecting data for five years, the researchers found a strong correlation between aflatoxin consumption and liver cancer. However, they needed more evidence to convince virologists, who already believed that the hepatitis-B virus was the most important contributor to liver cancer.

Essigmann, then a graduate student in Wogan's lab, made a key discovery that allowed the team to precisely measure aflatoxin exposure in humans, allowing them to prove the connection to liver cancer. Essigmann discovered that aflatoxin binds tightly to DNA, creating mutations that can lead to cancer. He and a graduate student, Richard Bennett, then developed a test that could detect the DNA-aflatoxin compound in urine.

Using that test, plus a blood test developed by Steven Tannenbaum, an MIT professor of biological engineering, the Wogan team could definitively track aflatoxin exposure. In 1992, two of his former graduate students, John Groopman and Thomas Kensler, now professors at Johns Hopkins University, published a study that conclusively linked liver cancer to the [toxin](#). "It really did drive the nail home in the argument. Even the virologists started to refer to aflatoxin as a risk factor," says Wogan.

Wogan later showed that exposure to both aflatoxin and hepatitis B dramatically boosts the risk of liver cancer by 60 to 100 times that of being exposed to either agent on its own. That synergistic effect is still unexplained.

Fighting cancer with broccoli

While working out the mechanism of aflatoxin's toxicity, Wogan kept his eye on his overarching goal: reducing the risk of [liver cancer](#), especially in developing countries, where aflatoxin is more frequently found in the food supply. His former students have carried on that legacy. In the late 1990s, Kensler found that a drug called oltipraz activates an enzyme that blocks aflatoxin's effects. A study he conducted in China, where aflatoxin exposure is common, found that giving the drug as a preventive measure dramatically reduced aflatoxin levels in the urine and blood.

However, oltipraz is prohibitively expensive, so the researchers looked for a dietary supplement that would do a same thing. It turns out that broccoli sprouts activate the same enzyme as oltipraz, so Kensler and colleagues are now studying the effects of a tea made from the sprouts. This has also reduced the amount of aflatoxin found in people who drink it.

Wogan, who founded MIT's Center for Environmental Health Sciences in 1978, still maintains a research lab at MIT, where he now focuses primarily on the cellular signaling molecule nitric oxide. However, three years ago, he, Essigmann and Tannenbaum resurrected their aflatoxin studies. This time, they're looking into a discovery Wogan made in the 1970s, that mice younger than 10 days old are very susceptible to aflatoxin exposure, but start to become resistant after 10 days.

By using the new tools of genomics and proteomics, the trio hopes to figure out what happens between the first and second weeks of life that makes the animals become resistant. "We can get lessons out of that that will teach us how to protect infants, and protect adults — it's a pure Wogan message," says Essigmann.

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