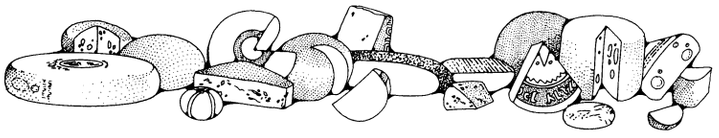
Cancer-Fighting Food Additives



Existing and potential food additives may offer an unexpected health bonus.

By JANET RALOFF

When the National Cancer Institute kicked off its "designer foods" program a couple of years ago, it announced the program would seek ways to reduce cancer risks via the diet. News accounts quickly focused on speculations by the program's first director about one day fortifying dietary offerings of otherwise questionable nutrition — such as cookies or chocolate bars — with food-derived, cancer-defying compounds.

Mark Messina, the designer-food program's new leader, won't rule out such products one day, but he isn't holding his breath. "It takes a lot of science to be able to do something like that," he notes, and "we're not at that point."

A nutritionist, Messina prefers to focus on whole foods rather than on any extractable magic bullets they may contain. One might even characterize his program as investigating recipes for the optimum anticarcinogenic salad: the most effective mix of cancer-fighting fruits, vegetables, seeds and oils.

However, the search for dietary magic bullets against cancer continues elsewhere. And several labs are reporting what they regard as very exciting candidates. One is a synthetic chemical widely used for decades as a preservative in everything from margarine to breakfast cereals. Another candidate, recently isolated from animal proteins, might substitute for conventional anti-staling food preservatives. And when added to raw ground beef, a pair of essential amino acids may even prevent potentially carcinogenic mutagens from forming during frying or broiling.

Additives aimed at fighting cancer will face many regulatory and safety hurdles before they reach the market. Indeed, the Food and Drug Administration has yet to approve the sale for use in food of even one non-nutritive ingredient aimed solely at improving health. But several agents do offer the tantalizing prospect that cooks and food manufacturers may one day impart cancer-fighting properties to foods lacking them.

In the United States, hamburger is a dietary staple. Each week families buy more ground beef at the grocery store than any other meat, according to a 1990 Bureau of Labor Statistics survey. Factor in restaurant purchases and U.S. hamburger consumption tips the scales at about 28 pounds per person annually.

However, this popular entree may pose a chronic cancer threat, a decade of research suggests. The same Maillard reaction that imparts a desirable flavor to meat as it browns during cooking also produces mutagens (SN: 7/11/87, p.25). "And it's been demonstrated by my group and [others] that these mutagens are rather powerful [animal] carcinogens — specifically affecting the breast and colon, and to a lesser extent the pancreas," notes organic chemist John H. Weisburger, director emeritus of the American Health Foundation in Valhalla, N.Y.

Because frying and broiling create only small quantities of these mutagens, their role in human cancer has not been established. "However," Weisburger says, "while the amount [of these mutagens] consumed at any one time is relatively small, in most instances the intake begins in childhood and occurs on an almost daily basis." Thus, he argues, it's only prudent to limit their consumption.

Toward this end, his lab tinkers with the chemistry of cooked meat in hopes of identifying agents that might arrest the mutagen's production.

His team announced its first success in 1982, after experimenting with a number of "filler" proteins to see if merely diluting ground meat would shut down mutagen formation. Substituting gluten, a mix of proteins found in cereal grains, for up to 10 percent of the hamburger cut mutagen formation when the meat patties fried. Making burgers from 10 percent soy protein and 90 percent ground beef entirely blocked the formation of frying-related mutagens, Weisburger recalls.

Because their data suggested that limiting mutagens involved more than simply diluting the meat, Weisburger's group decided to investigate what might be special about soy. Lacing raw burgers with pectin, a gelling compound in the soybean, dramatically inhibited mutagen formation during cooking. So did the soy's chlorogenic acid, a potent phenolic antioxidant that can slow or shut down oxidation — the potent and near-ubiquitous biologically damaging chemical reactions that involve the theft of an electron, usually from a protein.

The chlorogenic acid data encouraged the scientists to also test butylated hydroxyanisole, better known as BHA. Many manufacturers rely on this synthetic, phenolic antioxidant to prevent commercial food products from growing stale or rancid. Weisburger's team found it took even less BHA than chlorogenic acid — as little as 18 percent — to quash mutagen formation in cooking burgers.

In 1983, researchers in Sweden demonstrated that mutagen formation in cooking meat requires the presence of creatinine — a metabolic waste product widely distributed in muscle tissue. Weisburger and R. Conrad Jones, also at the American Health Foundation, responded with experiments aimed at neutralizing creatinine during cooking.

In 1988, the pair reported success: Coating the surfaces of raw patties with a sauce containing L-tryptophan, an essential amino acid, spared burgers from mutagen formation during pan frying. Indeed, their studies showed, chemicals that possess a structure known as an indole ring — including the essential amino acids L-tryptophan and L-proline — provide "a more specific means of lowering the formation of mutagens" than had the antioxidants.

Their current studies indicate that tryptophan and proline shut down mutagen formation by reacting with Maillard products before creatinine can. "We don't know the exact [chemical] nature of the Maillard products that react with creatinine or tryptophan," Weisburger told SCIENCE NEWS, but experiments suggest "they could be complex aldehydes" — organic compounds formed from alcohols.

Michael W. Pariza has made headlines in recent years with findings that a natural ingredient he isolated — first, from fried hamburgers (SN: 1/9/88, p.24), later from milk products including Cheese Whiz (SN: 2/11/89, p.87) — might fight cancer. Animal studies published in the Nov. 15, 1991 CANCER RESEARCH by the University of Wisconsin-Madison microbiologist and his co-workers now provide the first

evidence that dietary consumption of this substance "is effective in cancer prevention."

Their magic bullet is a fatty acid – conjugated linoleic acid (CLA) – one of the long-chain, carbon-based molecules from which fats and oils form. It bears an unusual structure, however, owing to a slight change in configuration that occurs during cooking.

Like normal linoleic acid, this polyunsaturated fatty acid contains a chain of 18 carbon atoms. But where the links in standard linoleic's chain possess a pair of double bonds separated by a pair of single ones, CLA has just one single bond between its pair of carbon double bonds.

The structural change alters CLA's pharmacologic properties.

Because they produce oxidizing free radicals, several polyunsaturated fatty acids (PUFAs) – including linoleic – can kill cells (SN: 5/21/88, p.332). In fact, many animal studies show that diets high in linoleic and other PUFAs can increase cancer risk. CLA, a powerful antioxidant, however, can quench free radicals. Animal studies now show that "it takes a lot more linoleic acid to enhance carcinogenesis than it does CLA to inhibit carcinogenesis," Pariza says.

In a six-month study intended to model human breast-cancer development, Pariza's team fed rats a chemical that spawns mammary cancers. The researchers found, however, that "CLA inhibits the development not only of malignant tumors, but benign tumors as well." Moreover, CLA is "more powerful than any other fatty acids or dietary fat ... in modulating tumor development." For instance, they note, while other scientists have shown that feeding high levels of fish oil (10 or 20 percent by weight of the diet) can halve the number of tumors in animals, just 5 to 10 percent as much CLA achieved the same tumor inhibition.

Because CLA does not stop tumor cells from growing, Pariza surmises that whatever benefits CLA consumption offers must occur "at a very early stage" in cancer development.

Pariza initially suspected CLA's cancer-fighting properties might trace to its effective quenching of biologically damaging oxidants. However, his data now indicate "there's more to CLA's anticancer effect than just the antioxidant effect. In fact, there's no direct evidence the two are even related."

When rats eat CLA-fortified diets, the fatty acid preferentially deposits in growing cells, such as those in developing mammary tumors. However, CLA's tumor-fighting effects do not appear due to a mere reversal of linoleic's cancer-promoting activities, Pariza says, because "CLA doesn't go into the tissue and kick linoleic out."

In a study using cultured cells exposed to benzo(a)pyrene, Pariza's team saw signs CLA might help detoxify the carcinogen. In their more recent mammary cancer study, the researchers found hints that CLA may also enter the membranes of tumor cells and somehow slow or rewire intercellular communications so the cells respond to growth cues less effectively.

"Hopefully, it won't be too much longer before we can say whether CLA is also likely to work [as an anticarcinogen] in people," Pariza says. And if it is? "It's possible that it could end up being used as a food additive," he ventures. After all, "our work documents in a very extensive way how nontoxic this stuff is." However, owing to the material's superior antioxidant properties, "it might well end up being used more because of its functional [food-preserving] properties than for cancer prevention."

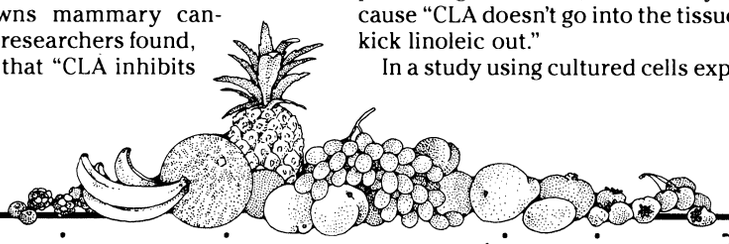
In the United States, mortality rates have plummeted for what had been two of the biggest cancer killers. Since the mid-1950s, stomach cancer deaths have dropped about 65 percent, and liver cancer deaths have fallen roughly 20 percent in women, 50 percent in men. Gary M. Williams, medical director of the American Health Foundation, suspects changes in the way Americans preserve food – such as a growing reliance on commercial antioxidants – has helped substantially.

Over the past quarter century, dozens of animal studies have demonstrated the ability of phenolic antioxidants – notably BHT and BHA – to inhibit chemically induced cancers in the lung, liver, forestomach, skin, breast and colon. However, doses of the antioxidants were relatively high – typically 5,000 parts per million (ppm) or more in the diet. Moreover, while an antioxidant often reduced cancer rates in one organ, it sometimes increased cancer risk in another.

Williams and his co-workers now report the first data showing that small doses of BHT – levels close to typical human exposures – can inhibit chemically induced liver cancers without increasing cancer risks elsewhere in the body.

For 18 months, most of the 350 rats in their study consumed chronic, low doses of a potent liver carcinogen, 2-acetylaminofluorene (AAF) together with between 0 and 6,000 ppm BHT. The antioxidant inhibited the early development of AAF-induced precancerous liver changes known as altered foci. By the end of the study, rats who received BHT at all but the highest dose also sported far fewer cancers than unsupplemented animals. Those receiving 3,000 ppm BHT showed precancerous bladder changes, however, and those consuming 6,000 ppm developed bladder cancers.

These data appear to indict BHT as a



When is a carcinogen an anticarcinogen?

First marketed in the 1950s, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) have become two of the most widely used food preservatives. Very effective antioxidants, they limit the development of objectionable flavors, color changes and rancidity in fats and baked goods.

These antioxidants have also protected animals from chemically induced cancers. Yet, at high doses, they sometimes promote the development of malignancies.

This apparent contradiction in their carcinogenicity illustrates a centuries-old maxim of toxicologists: Only the dose makes the poison. Agents safe in small amounts – such as table salt – may kill at extreme doses.

However, notes Robert Scheuplein, FDA's director of toxicological sciences, the Delaney Clause – a section of the Food, Drug and Cosmetic Act enacted in 1958 – makes no provision for this potential duality. It prohibits FDA from approving any food additive shown to "induce cancer" in humans or animals, regardless of the dose.

In its ability to tease out this duality, "science has gone beyond the [Delaney Clause] – and been beyond the law for 15 years," Scheuplein told SCIENCE NEWS. "But lately there's been so much data accumulating [to demonstrate that] that the pressures to do something about [the Delaney Clause] have gotten high."

Much of that pressure has focused on BHA and BHT. FDA has been reviewing the safety of both since 1980 – with an eye toward potentially banning them. Some factions within the agency believe in a strict interpretation of the Delaney Clause; Scheuplein and some others would prefer a more qualified interpretation – "such as whether you have a carcinogen at all at low doses."

The agency is currently about to issue a formal response to a citizen petition that it ban BHA, he notes. But Scheuplein says he has also asked his agency to fund an outside review of this additive's carcinogenity. – *J. Raloff*

weak carcinogen "of the promoter type," Williams and his co-workers report in the Dec. 1 CANCER RESEARCH. Nevertheless, they conclude, for protection against low exposures to weakly active carcinogens—such as cooking-related products—"BHT [supplementation] could have significant protective effects in the range of acceptable human doses, i.e., below 100 ppm."

These BHT data are so encouraging, Williams joked at an antioxidant conference in Tarrytown, N.Y., last October, that they "make me wonder whether there wouldn't be some merit to adding phenolic antioxidants to drinking water—like fluoride" — to supplement those already consumed in processed foods.

Other programs also have identified anticancer agents in and for foods:

• Topically applied tannic acid — an antioxidant in vegetable tannin — slows the growth of chemically induced benign skin papillomas and malignant skin carcinomas. The findings, to be detailed in the March CARCINOGENESIS, indicate this agent inhibits the promotion or proliferation of precancerous cells, explains cancer biochemist Jean-Pierre Perchellet of Kansas State University in Manhattan, who led the work.

• Myristicin, a major constituent of the oil present throughout parsley plants, may be considered "a potential cancer chemopreventive agent," researchers at LKT Laboratories in Minneapolis reported in the January JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY.

• Quercetin, a mutagen isolated from red wine, also appears to constitute one of the most powerful anticancer agents ever discovered, according to research by Terrance J. Leighton of the University of California, Berkeley. He says this compound, a major constituent in onions and garlic, may explain Chinese findings that people eating diets high in these vegetables suffer less stomach cancer.

• In experiments with lab-grown mouse and human cells, ellagic acid — a natural antioxidant in many fruits, nuts and trees — shields DNA from damage caused by tobacco smoke and other airborne carcinogens, say Gary D. Stoner and his co-workers at the Medical College of Ohio in Toledo.

• Antioxidant-rich green tea offers protection against cancers of the liver, lung, skin and digestive tract, animal studies indicate (SN: 8/31/91, p.133). Indeed, asserts Hirota Fujiki of the National Cancer Center Research Institute in Tokyo, quaffing this brew is "the cheapest and most practical method for cancer prevention available to the general public."

• NCI's Mark Messina prefers to push soybeans. These legumes contain a number of commonly available suspected anticarcinogens, such as phytate and protease inhibitors (SN: 3/28/87, p.206). They also provide a unique source of isoflavones—anti-estrogenic compounds that inhibit the products of cancer genes, he notes. What's more, he points out, unlike garlic, licorice, flax seeds and some other plant products being investigated by NCI's designer foods program, soybeans are not a condiment or flavoring but "an excellent protein" — one that can even lower serum cholesterol.

Perhaps the biggest take-home message of all, Messina believes, is the potential for reaping health benefits from non-nutritive plant-derived chemicals. Once considered irrelevant, he notes, "we're now seeing that there are hundreds that could be important." And that brings him back to arguing the importance of focusing on whole foods. At this stage of the science, he says, who can say that efforts to extract an apparent magic bullet may not leave more or better anti-cancer material to rot with scraps destined for the compost heap. □