

THE CASE AGAINST SUGAR

Amid calls to cut back or even ban added sugars, scientists hunt for alternative ways to **SATISFY OUR CRAVINGS**

STEPHEN K. RITTER, C&EN WASHINGTON

SUGAR IS TOXIC. The fat and sodium we've spent so much time fretting over may in fact be the lesser of the evils in our diet. New evidence suggests that sugar—and possibly artificial sweeteners—might be the ultimate cause of high blood pressure, high cholesterol, heart disease, diabetes, and liver disease.

Natural sugars in our diet aren't the ones on trial here. It's added sugars that are under greater scrutiny than ever before. Former New York City Mayor Michael R. Bloomberg's 2012 effort to curb the sale of supersized soft drinks put a spotlight on the added sugars in soda. But added sugars are prevalent in many foods and beverages:

coffee and sports drinks, juices, grain-based desserts, candy, and ready-to-eat cereals.

Naturally, the food and beverage industries—and the sweetener purveyors who supply them—officially disagree with sugar's bad rap. That position hasn't changed in 40 years. But they are increasingly looking for ways to reduce added sugars in their products by combining natural and artificial sweeteners, adding flavor enhancers to improve the taste of low- or zero-calorie sweeteners, and even searching for new kinds of sweeteners. They hope to avoid regulation as public health officials and government agencies consider ways to curb how much sugar we consume.

Some scientists, however, argue that the evidence against added sugar is so damning that we need to remove it from our diets entirely. Leading the crusade is endocrinologist Robert H. Lustig of the University of California, San Francisco. Lustig doesn't mince words when he calls sugar "the most demonized additive known to man."

Lustig coauthored a paper providing the basis for the American Heart Association's recommendation that men consume less than 150 calories (37.5 g or about 9 teaspoons) of added sugar per day. That's about the amount in one regular 12-oz soft drink. For women, the recommendation is less than 100 calories (25 g or about 6 teaspoons).

Although added-sugar consumption in the U.S. remains significantly higher than it was 50 years ago, the amount we take in has gone down during the past 15 years. Still, the average American consumes more than double AHA's recommendation—some 365 calories per day, according to the Department of Agriculture's Economic Research Service.

Not everyone thinks the case against added sugar is as clear as Lustig makes it out to be. Fergus M. Clydesdale, a food sci-

ence policy expert at the University of Massachusetts, Amherst, thinks that the data don't condemn sugar but rather suggest its moderation.

difference in how we metabolize natural and added sugars, the statement notes. But foods high in added sugars tend to be higher in calories and lower in essential nutrients and dietary fiber.

"In dealing with an obesity and public health crisis, the worst thing we can do is tell people not to have sugar," Clydesdale says. "A sweetened drink is fine once in a while. The biggest problem is that we are eating too darn much of everything. We've got to cut down."

SUGAR ESSENTIALS

Among added sugars the most common is table sugar, or sucrose. It's a disaccharide made of equal amounts of glucose and fructose and is typically derived from cane or sugar beet juice. In the U.S., high-fructose corn syrup (HFCS) is a close second. HFCS cropped up as a sweetener in the 1970s when sugar import tariffs and corn subsidies suddenly made it a cheap sugar substitute. Its introduction coincided with an increase in added sugar in the average American's diet.

HFCS is made by hydrolyzing the polysaccharides in cornstarch to form glucose

saccharides and in table sugar sucrose is a disaccharide. But that matters little because sugar's disaccharide breaks apart in the low pH of soft drinks and in the digestive tract.

Although this subject was once a source of heated debate, scientists, the sugar and corn trade associations, and consumer groups now agree that there is no significant nutritional difference between sugar and HFCS (*Physiol. Rev.* 2010, DOI: 10.1152/physrev.00019.2009). In fact, the three key dietary monosaccharides—glucose (starch sugar), fructose (fruit sugar), and galactose (milk sugar)—all have the same caloric count, 4 cal/g.

But there are differences once they enter the bloodstream. Insulin-regulated glucose is involved in getting energy into cells throughout the body, whereas insulin-independent fructose plays a role in glycogen, triglyceride, and cholesterol production in the liver. Meanwhile, galactose is converted to glucose in the liver.

Lustig suggests that abnormal spikes in sugar cause trouble by interfering with normal regulation of insulin, leptin, and ghrelin. These hormones control glucose and fat metabolism and signal hunger and the feeling of being full to the brain (*Nature* 2012, DOI: 10.1038/482027a).

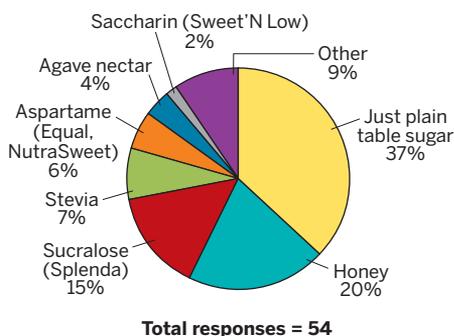
Lustig posits that fructose is the most damaging. Some fructose is converted to glycogen for immediate energy purposes, he notes. As with ethanol in alcoholic beverages, any excess is converted to liver fat. This can eventually overwhelm the liver, Lustig believes, leading to a condition known as insulin resistance.

The long-term result is fatty liver disease, Lustig says, which leads to obesity, heart disease, and diabetes. Lustig's review of global diabetes and nutrition data has convinced him that obesity does not cause diabetes—however, too much sugar does (*PLOS One* 2013, DOI: 10.1371/journal.pone.0057873).

Given the complex biochemistry of the human body, Lustig's theory may be hard to prove experimentally. But in one research study, genetically engineered mice unable to metabolize fructose appeared to be protected from these health problems (*Nat. Commun.* 2013, DOI: 10.1038/ncomms3434).

Critics note that most studies of the health effects of added sugar have looked at animals, not humans. The handful of human studies done so far draws on national surveys. As such they provide only correlations between sugar and health outcomes.

WE ASKED READERS, "What sweetener do you prefer?" They responded via Facebook and Twitter. If you missed the poll but want to weigh in go to <http://cenm.ag/sugarpoll>.



"I can't stand nonsugar sweeteners."

—CATHY BLOEDORN, FACEBOOK

"Sugar because it doesn't give a swimming pool aftertaste."

—WALT DICENY, TWITTER

"Maple syrup because of its supreme deliciousness."

—CHRIS TAYLOR, TWITTER

and then enzymatically isomerizing most of the glucose to fructose. The industry started calling the sweetener "high-fructose corn syrup" to indicate that during processing the fructose level reaches 90%. But in the formulations most commonly used in foods and beverages, the final fraction of fructose is adjusted down to 55% or 42% by diluting with more glucose.

As a consequence, its glucose-fructose ratio is not so different from that of table sugar, except in HFCS the sugars are mono-

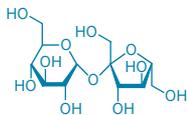
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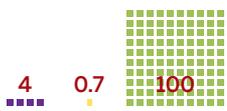
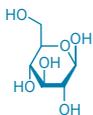
A SWEET SAMPLER The innate human need to taste something sweet has led to the development of many sweeteners.

Bulk sweeteners

Sucrose (table sugar)



Glucose (dextrose)



Others: trehalose, galactose, maltose, lactose, brown rice syrup, barley malt syrup, molasses

Honey



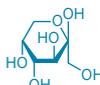
Maple syrup



Agave syrup



Fructose

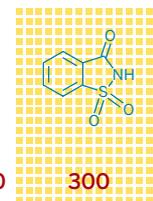


High-fructose corn syrup (fructose:glucose = 55:45)

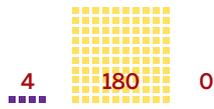
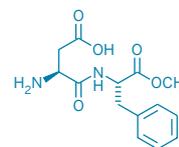


Artificial sweeteners

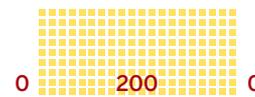
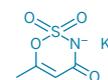
Saccharin (Sweet'N Low)



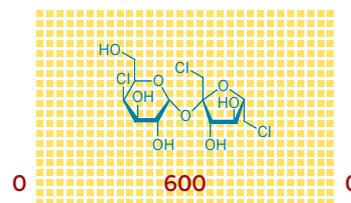
Aspartame (NutraSweet, Equal)



Acesulfame-K (Sweet One, Sunett)



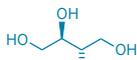
Sucralose (Splenda)



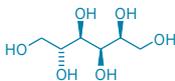
Others: neotame, cyclamate, advantame

Sugar alcohols (polyols)

Erythritol



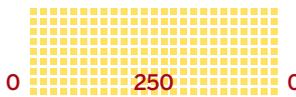
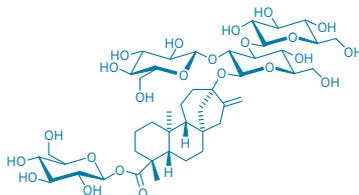
Sorbitol



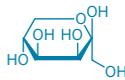
Others: xylitol, maltitol, mannitol, isomalt, lactitol

New sweeteners

Rebaudioside A or stevia (Truvia, Pure Via)



Tagatose



Others: Norbu (mogroside from monk fruit)

Key: ■ Calories per gram ■ Sweetness index^a ■ Glycemic index^b

Glycemic index of common foods



Baked potato, 110



Cornflakes, 90



White rice, 89



White bread, 70



Apple, 39



Black beans, 30

NOTE: Most common sweeteners are mentioned; there are many others out there. **a** Relative to sucrose. **b** A measure of how much a food raises a person's blood glucose; glucose is defined as 100. **SOURCES:** sugar-and-sweetener-guide.com, International Table of Glycemic Index & Glycemic Load Values, glycemicindex.com, company data

For example, a study published earlier this year evaluating data from the National Health & Nutrition Examination Survey found that the average American derives 14.9% of their calories from added sugar. Those who derived 17 to 21% of calories from added sugar had a 38% greater risk of dying from cardiovascular disease compared with those who consumed only 8% of their calories from added sugar (*JAMA Intern. Med.* 2014, DOI: 10.1001/jamainternmed.2013.13563).

CUTTING BACK

An obvious way to reduce added sugar is to rely more on artificial sweeteners. Their intense sweetness means we can use less. But this switch may not have the intended benefit, according to Purdue University behavioral neuroscientist Susan E. Swithers, who studies correlations between eating and weight management.

“Substituting a part of the diet with a similar-tasting item that has fewer or zero calories sounds like a common-sense approach to lose weight and possibly improve health,” Swithers says. “But common sense is not always right.”

When the mouth tastes something sweet, it tells the body to prepare for the calories, Swithers notes. But when those calories aren’t present, she believes the body’s mechanisms to control food intake become ineffective.

Swithers points to Russian digestive physiologist Ivan Pavlov’s research on conditioned responses to explain. In Pavlov’s classic experiment, he learned that making a sound when giving food to a dog would condition the dog to associate the sound with the presentation of food. When hearing the sound, the dog would salivate whether the food was delivered or not.

“Pavlov demonstrated that there are many cues—when we see and smell something and then when it hits our mouths—that trigger physiological responses and help us prepare for what is going to arrive in our bodies,” Swithers says. “So if we trick the mouth and interrupt that conditioned response with an artificial sweetener, it is going to be problematic.”

Swithers reviewed research studies that explored links between consuming zero- or low-calorie sweeteners and overeating, weight gain, and health problems. She concluded that people who consume artificially sweetened beverages don’t have any better

health outcomes than people who don’t.

To test the idea, Swithers and her team have observed that rats consuming a noncaloric sweetener, such as saccharin-sweetened yogurt, failed to adjust their food intake to account for the sweetener’s lack of calories. The animals overate and gained more weight than rats receiving sugar-sweetened yogurt.

Swithers says the inability to accurately predict the arrival of energy in the gut appears to weaken the cascade of hormone-controlled events that leads to the feeling of being full. Swithers has also observed this unexpected effect in lab animals with fat substitutes used in snack foods.

Additional evidence comes from functional magnetic resonance imaging studies of the brain. In one example, Erin Green

have oversweetened our food supply. It’s important that the public understands the science in order to help them make the best health decisions.”

NEW OPTIONS

Consumers seem to be getting the message. People in the U.S. have been shifting away from carbonated soft drinks and toward bottled water, tea, and energy drinks for years. But they defected at an even faster rate in 2013, according to data reported by *Beverage Digest*, an industry newsletter. Per capita consumption of carbonated soft drinks is at its lowest level since 1986.

But that’s not to say our appetite for added sugar is gone. Far from it. To satisfy the innate urge to eat something sweet, scientists and manufacturers are looking for ways to reduce sugar in the products we love.

It’s a difficult problem. “Sugar plays many functional roles in foods and beverages, from taste to providing the texture of creamy foods and the appealing browning of baked goods,” Clydesdale says. Artificial sweeteners, such as saccharin or sucralose, are more intense so we use less. They are also zero calorie and don’t increase blood glucose levels, which are blessings to diabetics. But they can’t replace all of sugar’s properties, he notes.

And they can come with an objectionable bitter aftertaste. As humans evolved, the need to identify nutritious foods such as fruits, vegetables, and grains resulted in a single sweet-taste receptor in the taste buds on the tongue—a G protein-coupled receptor dimer known as T1R2/T1R3. But the ability to taste something bitter, often a sign of toxicity, was perhaps more important: Humans have some 25 bitter receptors.

About a decade ago, when scientists began to better understand these receptors, they started to use high-throughput screening techniques to identify new sweetener additives that might block the bitter aftertaste of artificial sweeteners. They’ve used the same methods to find additives that might enhance the sweetness of sugar and HFCS. The technology is allowing scientists to come up with sweetener taste packages that optimize the desired sweet taste with fewer calories.

For example, Givaudan’s TasteSolutions line of flavor ingredients includes

SWEET TOOTH The American Heart Association’s added sugar recommendations

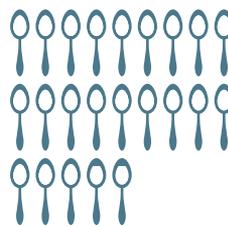
Women limit added sugar to 100 calories per day or about 6 teaspoons



Men limit added sugar to 150 calories per day or about 9 teaspoons



The average American actually consumes 365 calories per day or about 23 teaspoons



and Claire Murphy of San Diego State University and the University of California, San Diego, compared people who regularly drank diet sodas with those who didn’t drink diet sodas.

While brain scans were under way, the researchers randomly had study participants sip sugar water or saccharin water. The reward-processing regions of the brain that lit up differed sharply, depending on past diet drink consumption, not what the participants were drinking at the time. According to Swithers, the findings suggest that, once fooled, the brain’s sweet processing system may no longer be able to reliably gauge calorie intake.

“I am a scientist, but I am also a consumer, so it is hard to differentiate sometimes my scientific versus my personal opinions,” Swithers admits. “But it is clear we

4-(2,2,3-trimethylcyclopentyl)butanoic acid, which reduces the bitterness of artificial sweeteners (*Curr. Biol.* 2010, DOI: 10.1016/j.cub.2010.04.043). Senomyx's Sweetmyx products include heterocyclic compounds such as aryl-substituted thioureas and benzothiadiazines, which have structures that resemble saccharin and improve sugar's sweetness (*Proc. Natl. Acad. Sci. USA* 2010, DOI: 10.1073/pnas.0911670107).

But scientists continue to hunt for a natural sugarlike molecule that is low-cal, tastes the same as sugar, and imparts the same functional properties.

One popular alternative is stevia. Originating in South America, the stevia plant has been used as a sweetener in some countries for years. In the past decade, scientists have managed to isolate a series of the plant's sweet-tasting glucose-coated diterpene molecules, called steviol glycosides. Rebaudioside A, the version with the most preferred taste profile, is more than 200 times as sweet as sugar and has little or no effect on blood glucose levels. The sweetener is available in Cargill's Truvia used by Coca-Cola, PureCircle's Pure Via used by PepsiCo, and others.

Stevia's taste has a slower onset, and it retains its sweet taste longer than sugar. But at high concentrations it imparts an unfavorable aftertaste. To counter that, Truvia, for example, is made up of 90% erythritol mixed with rebaudiosides and natural flavor additives. Erythritol is a sugar alcohol commonly used as a bulking agent to take up dead space so that artificial sweeteners behave more like sugar. Erythritol is about 60% as sweet as sugar, and at 0.2 cal/g has 5% of the calories, which is low enough to be considered zero calorie on nutrition labels.

Just as they did with saccharin, cyclamate, and other artificial sweeteners, regulatory agencies and consumer advocacy groups have questioned stevia's safety. Although stevia has stood up to this scrutiny, the search for alternatives continues.

Another promising sweetener is tagatose, a stereoisomer of fructose. Unlike fructose, tagatose is a little less sweet than sugar. But it has a calorie count of 1.5 cal/g relative to sugar's 4 cal/g and only slightly affects blood glucose levels, according to Yang Hee Kim, a senior scientist at CJ CheilJedang, a South Korean sweetener producer. The company is trying to introduce tagatose to a global market.

The minor structural difference between fructose and tagatose means that

tagatose doesn't bind to digestive enzymes the same way and is not fully metabolized. Tagatose controls blood glucose levels, Kim explains, because it inhibits carbohydrate digestion in the small intestine and promotes glucose conversion to glycogen in the liver. In taste tests people rate the sweetness and texture of tagatose and sugar as being about the same, she notes.

Tagatose also functions well in ice cream and soft drinks, Kim says, and it produces good browning for baking. However, it exists in small amounts in nature. CJ CheilJedang has therefore developed a two-step process to produce tagatose from the disaccharide lactose derived from milk processing. Lactose is first hydrolyzed into galactose and glucose by β -galactosidase,

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and then galactose is converted into tagatose by L-arabinose isomerase.

The company currently produces 2,000 metric tons of tagatose per year for table consumption. But Kim is enthusiastic about the prospects of tagatose catching on as a full sugar replacement.

Scientists are also taking a closer look at natural sweeteners such as honey, maple syrup, and molasses. Beyond their primary constituents glucose and fructose, these sweeteners contain other classes of bioactive compounds including complex carbohydrates, amino acids, and polyphenols that might impart health benefits, scientists have found (C&EN, April 14, page 10).

The complex carbohydrates in particular could offer a sweet advantage. For example, earlier this year at the American Chemical Society national meeting in Dallas, Mercedes G. López of the Center for Research & Advanced Studies of the National Polytechnic Institute, in Mexico, described studies on the composition and potential health benefits of agavins, which are branched polysaccharides (a type of dietary fiber) found in agave, the plant used to make tequila.

Agave syrup, which has become a popular sweetener recently, is obtained by cooking down the raw plant and is about 85% fructose monosaccharide. Being high in fructose is not particularly desirable, López admits. But agavins are mildly sweet with no aftertaste. And the largely nondigestible fiber would not be expected to raise blood glucose, but it would help people feel fuller so they would eat less.

López and her team wondered whether agavins might have beneficial effects similar to inulin, a related polysaccharide found in wheat, bananas, and other plants. Inulin has been shown to help increase insulin secretion and has been used as a sugar substitute by diabetics for years. It is also now being used as a bulking agent in some stevia-based sweeteners.

The researchers found that mice receiving agavin supplements in their water eat less, gain less weight, and have lower blood glucose levels compared with mice that consume sweeteners such as sugar, agave syrup, and aspartame. Agavins also increase levels of glucagon-like peptide-1, a hormone that slows the stomach from

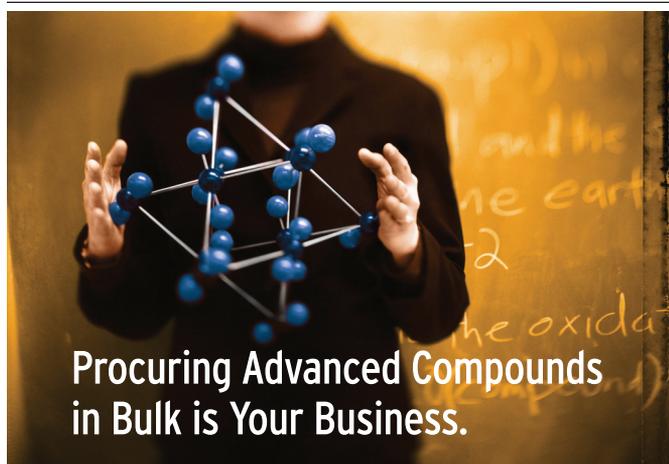
emptying and stimulates production of insulin. López thinks they are promising. “Our study represents the first attempt to evaluate agavins as sweeteners,” she says.

PUBLIC PRESSURE MOUNTS

No matter how many substitutes become available in the attempt to improve on sugar, society’s current means of sweetening its food isn’t ideal. Public officials and health regulatory agencies are under pressure to start finding solutions.

Two-thirds of the nearly 1,300 respondents to a 2013 *New England Journal of Medicine* poll favored government regulation of sugar (DOI: 10.1056/nejmclde1215057).

But opposition remains, as New York City’s experience shows. A judge blocked implementation of Bloomberg’s proposed regulation on sugary soft drinks because it was not uniformly enforceable. Meanwhile, industry, advocacy groups, and others argue that a 16-cal spoonful of sugar should be an unalienable right alongside



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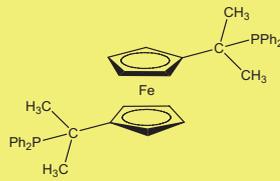
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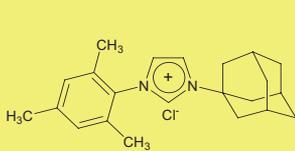
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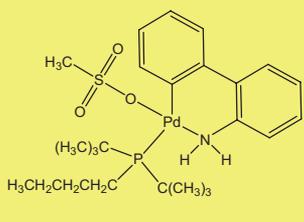




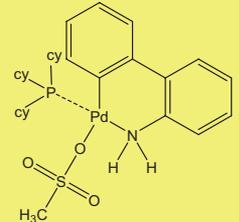
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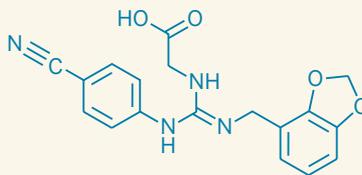
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The range of public opinion represented in the *NEJM* poll varied widely. Some believe personal responsibility should be enough to control our sugar diet without limits or an outright ban. Yet others point out that all of society must bear the consequences of too much sugar, which include rising health care costs, lost wages, and reduced productivity.

UC San Francisco's Lustig is more blunt. Sugar has gone from being a condiment to a dietary staple, Lustig says, and he thinks it should be controlled like a narcotic. "If a substance is abused and addictive and it contributes to societal problems," he contends, "that's criteria for regulation." Lustig believes sweeteners should at least be removed from the Food & Drug Administration's "generally recognized as safe" list.

UMass's Clydesdale suggests that instead of worrying about controlling added sugar, fat, and sodium, "we should concentrate on having people eat differently." Food science has given us excellent-tasting low-cost fresh, frozen, and canned prepared foods that contain vegetables and protein and are low in fat, sodium, and added sugar, Clydesdale says. "But the public backlash against processed foods is preventing their broader adoption. I find it a great frustration that people line up to buy the latest electronic gadgets but they aren't lining up to buy the latest in food technology."

Part of the problem is that the economic incentive for buying foods is currently upside down, Purdue's Swithers believes. "It is often cheaper to buy processed foods and eat at fast-food restaurants than it is to buy fresh foods at restaurants or to prepare them at home. From a public health policy

perspective, that needs to be addressed."

She points to lessons learned from reducing sodium to meet recommended healthy levels in the diet. When salt is not added to processed or fresh prepared food, and the consumer is given a saltshaker to add as much salt as they want, people tend to use less salt overall, Swithers notes. She thinks this behavior would hold for sugar as well.

Swithers also points to lessons learned with tobacco. Cigarettes have known negative health consequences and no real health benefits, she says. The use of age restrictions, higher taxes, scare-tactic labeling, and peer pressure have drastically curbed smoking, making it unnecessary to resort to an outright ban. Swithers thinks that public health and government agencies could use the same strategies to reduce the use of natural and artificial sweeteners.

"It might be a so-called nanny state," Swithers says, "but I don't think it is unreasonable as a start to tax sweetened beverages, to restrict the size so that buying more is more expensive, and to curtail advertising and marketing to children." ■

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