No one knows why humans evolved with the ability to detect sweetness. Perhaps it enabled us to recognize fruits that were ripe and therefore richer in useful carbohydrates. Because sweetness is often linked to high calorie foods, a sweet tooth could be useful in a primitive world. However, in today's wealthy countries where there is too much food, sweetness can lead us into a trap. Using sucrose to satisfy our craving for sweet things, we accelerate tooth decay and run the risk of getting fat.

The challenge for chemists seems simple: Find other molecules that are sweet but have no calories. This is easier said than done. Until recently there were two difficulties. First, chemists had no idea which parts of a molecule make it sweet. Second, if the sweet part were found, the chances of making a molecule that contained the sweet part, yet was different enough to have no calories and still be safe to eat, were very slim. The first artificial sweetener illustrates the problems.

Heavy sweetener
More than 2000 years ago the Greeks and Romans found that boiling grape juice in lead pans produced a syrup that was intensely sweet. This was because it contained lead acetate, Pb(CH₃COO)₂·3H₂O, which is very sweet and was once called "sugar of lead." Blissfully unaware that lead is toxic, cooks of the Roman Empire used sapa, their name for the sweetener, to flavor their foods. It was also used to sweeten and preserve wine. Some modern historians have suggested that the decline of the Roman Empire was caused in part by too much lead in the diet and a resulting decrease in birthrates.

The next sweet-tasting chemical to be discovered was beryllium. Salts of this metal taste sweet, and the first name given to the element was glaucinum, meaning sweet. But, like lead compounds, those of beryllium are poisonous, and they were never widely used as sweeteners.
First substitute
The first break in artificial sweeteners came when saccharin (Figure 1) was prepared in 1879 at Johns Hopkins University, Baltimore, Md., by Ira Remsen and Constantin Fahlberg. Saccharin was hailed as a boon to diabetics, whose strict avoidance of sugar denied them sweetness in their diet, and was submitted to safety tests. In one test diabetics ate 5 g of saccharin a day for 150 days without reporting any ill effects. Since the saccharin tablets used for sweetening coffee and tea usually contain 15 mg of the sweetener, this is equivalent to using about 330 of the tablets a day! For the short term, at least, saccharin was proven safe. However, many frowned on saccharin use. Sugar was considered particularly pure and wholesome, so it was thought that food and candy makers were reducing the food value of their products by using saccharin. Saccharin was soon banned in several European countries, despite tests showing it was safe. The world's first practical artificial sweetener was embroiled in controversy.

In 1912 President Roosevelt set up a review board to examine saccharin. The board concluded that it was safe to take 0.3 g daily, which is equivalent to six ounces of sugar. With this presidential seal of approval, the way was open for saccharin to be used in all sorts of foods.

Saccharin was especially useful during the two world wars. With sucrose in short supply, real sugar was added to the rations destined for soldiers, who needed the caloric energy, and the folks at home made do with artificial sweetness. Yet saccharin did not become popular until the modern fashion for slimness came into vogue around 1950. Even though the idea of

Figure 1. Sulfur and nitrogen bring sweetness to some molecules.
How sweet is it?
Relative sweetness, compared to an equal mass of sucrose.

<table>
<thead>
<tr>
<th>Sugar</th>
<th>Sweetness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrose</td>
<td>1</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.7</td>
</tr>
<tr>
<td>Fructose</td>
<td>1.3–1.8</td>
</tr>
<tr>
<td>Cyclamate</td>
<td>25</td>
</tr>
<tr>
<td>Saccharin</td>
<td>300</td>
</tr>
<tr>
<td>Aspartame</td>
<td>200</td>
</tr>
<tr>
<td>Acesulfame</td>
<td>200</td>
</tr>
</tbody>
</table>

a chemical sweetener had been accepted, it was nearly 60 years after the discovery of saccharin before another sweetener was found—cyclamate.

Cyclamate (Figure 1), like saccharin, was discovered accidentally. While Michael Sveda of the University of Illinois was working with the compound, he momentarily rested his cigarette on the lab bench, returned it to his mouth, and found that it tasted extremely sweet. The cigarette had picked up a tiny crystal of cyclamate.

Another sweetener—a relative of saccharin—was discovered in almost the same way. In 1967 Karl Claus, a chemist at the German company Hoechst, licked his fingers in order to pick up a filter paper. Claus had discovered acesulfame (Figure 1), a chemical that is now popular in Europe, where it is known commercially as Sunnett. Sunnett is not currently used in the United States, although the U.S. Food and Drug Administration (FDA) has been petitioned for its approval. Needless to say, this method of discovering chemicals is very risky—and could be fatal!

Turns sour
Things began to go wrong for cyclamate in 1957 when a research team in England reported that mice exposed to cyclamate developed cancer. The study did not impress the

Sucrose
Sugarcane, known in India 5000 years ago, was transported to southern Europe in about 800 A.D. It gained popularity as a major world crop after Columbus took some on his second voyage to the West Indies. Sugar beets, another source of sugar, were developed in Europe about 1800 A.D. Sugarcane thrives in warm, moist climates such as Hawaii, whereas sugar beets are a suitable source for sugar in cooler climates such as Idaho.

Common table sugar, sucrose, is refined from sugarcane and sugar beets. It is a double sugar (disaccharide) composed of two smaller sugar molecules—glucose and fructose. Sucrose can be split to yield these smaller sugars by reaction with acid or an enzyme (invertase) to yield a mixture known as "invert" sugar. The O—H group on the sucrose carbon atom 4 is part of the "triangle of sweetness" because, if the sucrose molecule is reconstructed so that this group is upward instead of sideways, then all sweetness is lost. Other atoms that must not be tampered with are the O—H's on carbons 2 and 1'. This indicates that there is probably more than one triangle of sweetness in the sucrose molecule.
FDA at the time because of the extreme test conditions—cyclamate pellets had been implanted in the mice bladders—but the seeds of doubt had been sown. In 1970, other tests showed that rats fed high doses of cyclamate developed bladder cancers slightly more often than normal, and this sweetener was banned. Similar tests with saccharin were carried out with comparable results, and saccharin too was banned in Canada in 1977. The poor rats, however, had to eat very large amounts of saccharin—comparable to a human drinking 800 cans of artificially sweetened cola each day—and many observers found the animal experiments unconvincing. Studies on humans supported saccharin’s safety. To this day saccharin is used all over the world and is a very popular artificial sweetener. Several countries also found the cyclamate tests unconvincing, so this sweetener is still on sale in Europe and Australia. Even Canada lifted its ban a few years later, but cyclamate is still forbidden in the United States and the United Kingdom (although a petition is under review for cyclamate’s approval in the United States). One of the problems with cyclamate is that, although it is about 25 times sweeter than sugar, it has only one-tenth the sweetening power of saccharin; therefore, cyclamate has to be used in greater quantities.

**Safe at the plate?**
Saccharin, cyclamate, and ace-sulfame are all sulfur–nitrogen sweeteners—are they safe? It appears the answer is yes. In 1979, again at Johns Hopkins University, a study of the eating habits of 500 people with bladder cancer showed no link with the use of saccharin and cyclamate. In theory these artificial sweeteners should be safe because they pass through the body easily and are not metabolized (changed). The chance of getting cancer from them is extremely small, if it exists at all.

The most successful artificial sweetener of the 1980s is aspartame (Figure 2), which was discovered in 1965 by James Schlatter while researching anti-ulcer drugs for the pharmaceutical firm G.D. Searle & Co. The aspartame molecule consists of two amino acids joined together. Unlike most artificial sweeteners, aspartame is metabolized in the body. The amino acids of which it is composed, aspartyl and phenylalanine, are nutritional and caloric. Yet the sweetener itself is considered low-calorie because it is intensely sweet and can be used in small quantities. There are a few people, however, who cannot metabolize phenylalanine because of a genetic disorder. One person in 15,000 has this problem, called phenylketonuria (PKU). Most people who have this disorder are aware of the danger and know how to manage it by carefully avoiding taking in an excess of phenylalanine. Aspartame, known as Equal in the supermarket and NutraSweet when used by food manufacturers, is safe to use for the remaining 99.994% of the population.

**Nature’s secret**
What makes a molecule taste sweet? The obvious answer is the molecular shape. We know the shape of the molecule is important because there are some molecular “twins”—called mirror isomers—in which one tastes sweet but the other does not. An example is phenylalanine (Figure 3).

The D-phenylalanine isomer is sweet (sweeter than sugar) but L-phenylalanine actually tastes bitter. These molecules have the same atoms, the same formula, and, at a glance, can be mistaken as identical. However, the arrangement of atoms in the D-isomer is the reverse—the mirror image—of the arrangement of the L-isomer. Both molecules trigger receptors in our taste buds, but the D-isomer triggers the sweet receptors,
This corner must be an N−H or O−H group that seeks to form a hydrogen bond with O or N atoms in the tongue’s receptors.

Corner B needs to be a basic atom (O or N) that can attract N−H or O−H centers in the receptor.

Corner C should be any group that repels water, such as CH₂, CH₃, or C₆H₅.

**Figure 4. Triangle of Sweetness.**

whereas the L-isomer triggers the bitter. The conclusion is inescapable: Sweetness is not caused by a particular element or elements (D- and L-phenylalanine have the same elements); it must be caused by a certain shape.

**The shape search**

Today we know of about 50 sweet-tasting molecules, and these have been studied to see if they have a common factor—and they do. The result is a new chemical theory of sweetness, the triangle theory. This theory asserts that there are three sites in a molecule that are responsible for sweetness. Apparently these three sites give the molecule the proper structure to lock onto the taste buds, where it presses the three-key code that registers “sweet” in our brains. Two of these keys are triggered by the formation of hydrogen bonds.

The receptors of our taste buds are composed of proteins, which have the ability to form hydrogen bonds with other molecules. Hydrogen bonds are attractions between certain hydrogen atoms and more electronegative atoms, such as oxygen. The proteins have N−H and O−H groups that can offer their H, and C=O groups whose oxygen attracts the H. The hydrogen bonds are often represented as dots, such as C=O...H−N and C=O...H−O. (See the hydrogen bonds in the box “Sucrose.”) Sweet molecules must have hydrogen bond donors such as O−H and N−H, and hydrogen bond acceptors, such as oxygen or nitrogen, that match the donors and receptors in the taste buds. But hydrogen bonding ability is not enough.

Lemont Kier of the Massachusetts College of Pharmacy, Boston, realized that a third factor is involved in sweetness. The molecule must have another site that is actually repellant to hydrogen bonding, the so-called hydrophobic site. Kier identified the third side of a “triangle of sweetness” that triggers the sweet taste bud (Figure 4). The triangle has a specific arrangement of a hydrogen bond donor site (triangle corner A), an acceptor site (corner B), and a hydrophobic site (corner C).

Not only must the molecule have these three sites, but they must be separated from one another at certain distances. Of course molecules are three-dimensional, and it is not obvious from a two-dimensional drawing whether a triangle of sweetness is present. Also, many molecules are flexible and some have many O−H groups and oxygen atoms. This makes it challenging to locate the triangle. For example, in the sucrose molecule there are eight O−H groups that could serve as corner A of the triangle, 11 oxygen atoms that could be corner B, and three CH₂ groups that could act as corner C.

**Canine sweet tooth**

There are some molecules that are over a thousand times sweeter than sucrose. Thaumatin, derived from the West African plant ketemfe (Thaumatococcus danielli) is 3000 times as sweet. This compound is a peptide polymer with so many triangles along its length that it locks onto many receptors and stays a long time—too long. Ideally, a sweetener should register instantly but not linger on the tongue. Thaumatin is used in chewing gum and unpleasant-tasting medicines, when a lingering sweetness is desirable, and in some pet foods to encourage animals to eat meats that are less than appetizing.

Artificial sweeteners are big business. In the few years aspartame has been on the market sales have climbed to $1 billion a year worldwide, and they are expected to double in the next five years. But, it seems, every artificial sweetener has some drawback. When aspartame is heated it readily hydrolyzes (splits into two amino acids) and loses its sweetness. Thus aspartame is not suitable for baking and cooking, but it is ideal for diet soft drinks. In this area aspartame has rapidly displaced saccharin, which has a bitter aftertaste that is hard to eliminate. Blends of aspartame and saccharin are sometimes used to disguise the aftertaste of saccharin.

The world is still waiting for a better sweetener, and perhaps the theory of the “triangle of sweetness” will now make it possible to custom design the perfect sweetener. What is the perfect sweetener? It’s about as sweet or sweeter than sucrose, nontoxic, quick to register its taste but doesn’t linger, has no calories, is inexpensive to make, and is stable when dissolved in water or cooked at high temperatures. Find a compound that meets these specifications and a fortune is yours.

**John Emsley** is a Reader at King’s College, University of London. He is a regular contributor to New Scientist, a weekly science magazine published in Great Britain.

**REFERENCES**

