ASPIRIN

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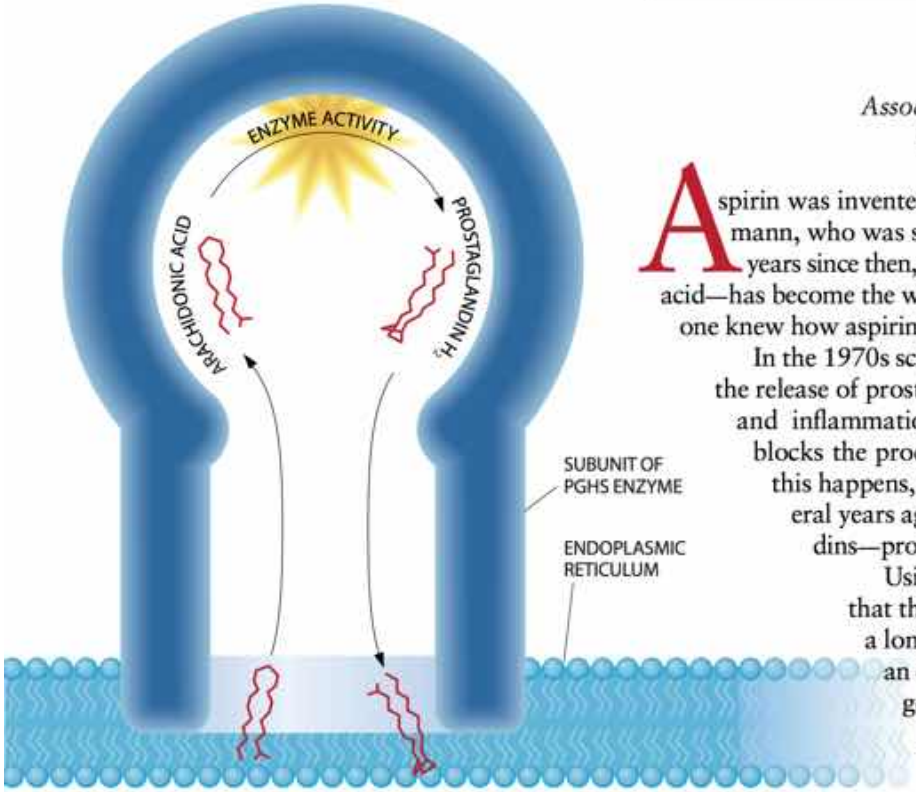
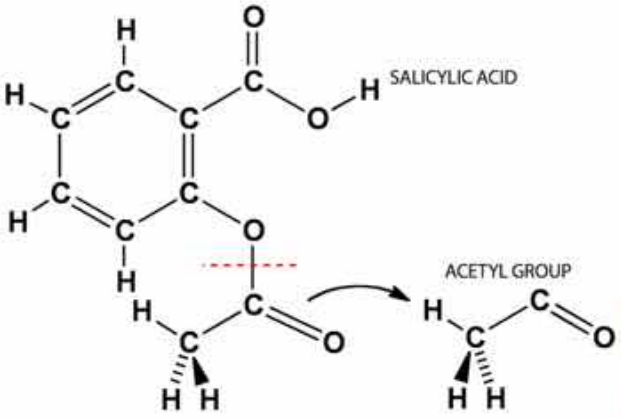
Aspirin was invented in the late 1890s by German chemist Felix Hoffmann, who was seeking to ease his father's arthritis pain. In the 100 years since then, aspirin—or as it is known to chemists, acetylsalicylic acid—has become the world's most widely used drug. But until recently, no one knew how aspirin actually works.

In the 1970s scientists learned that injuries to human tissue trigger the release of prostaglandins, hormonelike molecules that cause fever and inflammation. They also discovered that aspirin somehow blocks the production of these molecules. To reveal exactly how this happens, a team of researchers, including myself, began several years ago to analyze the enzyme that produces prostaglandins—prostaglandin H_2 synthase, or PGHS.

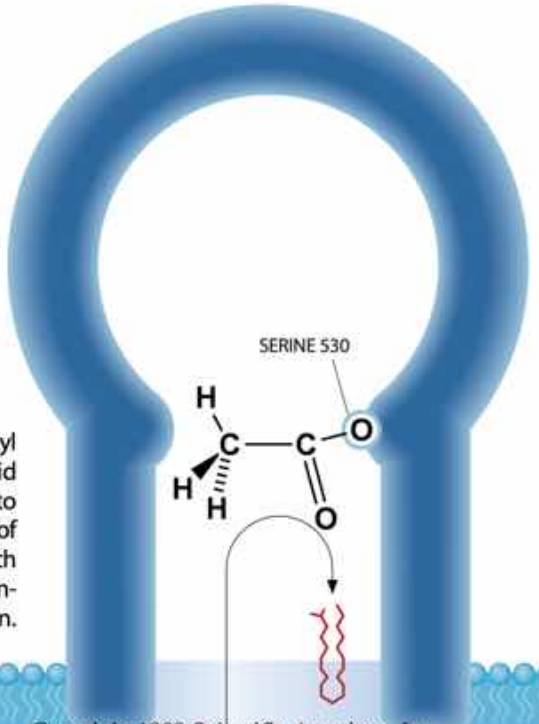
Using x-ray analysis of PGHS crystals, we discovered that the enzyme contains two protein subunits, each with a long interior channel. Molecules of arachidonic acid—an essential fatty acid—enter these channels and undergo a chemical transformation in the enzyme's core, converting to molecules of prostaglandin H_2. Aspirin prevents this change by sealing the channels: the aspirin molecule's acetyl group binds to a site inside the channel, blocking the path of the arachidonic acid. Other anti-inflammatory drugs, such as ibuprofen and naproxen, work by physically plugging the enzyme's channels rather than chemically altering them.



PGHS ENZYME produces the prostaglandins that cause fever and inflammation. Arachidonic acid from the endoplasmic reticulum, an internal cell membrane, moves through a channel to the core of the enzyme, where it is converted to prostaglandin H_2.



ASPIRIN MOLECULE contains an acetyl group linked to salicylic acid, including atoms of carbon (C), oxygen (O) and hydrogen (H). When aspirin enters the interior channel of the PGHS enzyme, the molecule splits in two, with the acetyl group binding to a site inside the channel and the salicylic acid usually floating away.



NEW CONFIGURATION of the PGHS enzyme—with the acetyl group bound to a site called serine 530—blocks arachidonic acid from the core of the enzyme, thus preventing its conversion to prostaglandin H_2. Unfortunately, aspirin shuts down all forms of the PGHS enzyme, including the form that protects the stomach lining. Drug companies are now developing a new class of painkillers that target only the form of PGHS that causes inflammation.

GEORGE RETSECK AND BRYAN CHRISTIE