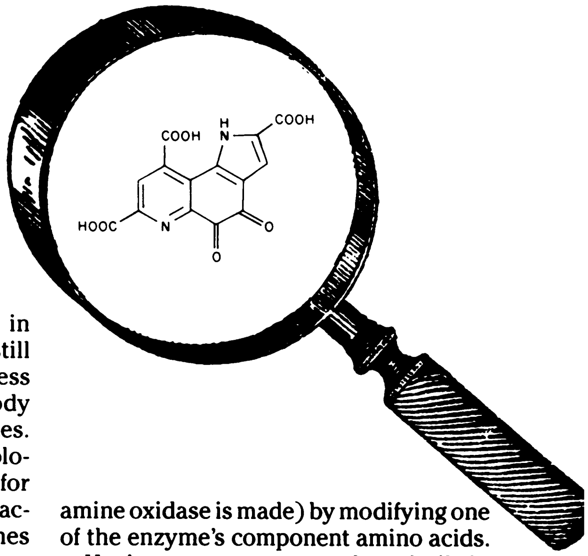
Vitamin or Just Vital?

Cryptic molecule leads scientists in circles



By WENDY GIBBONS

Here follows a tale of chemical trickery. It's the saga of a compound so elusive that it repeatedly misled sleuths who suspected it might prove to be the first newly discovered vitamin in more than 40 years. The theme: Scientific enigmas don't die easy.

With a little tailoring, roughly half of the 13 known vitamins can function as coenzymes – helper molecules that enable enzymes to perform their handiwork in the body. For example, pyridoxal, better known as vitamin B6, collaborates with an enzyme that breaks down a form of starch into sugar.

Until recently, nutritional chemists assumed they had identified all of these helper molecules, says Judith P. Klinman, an enzymologist at the University of California, Berkeley. "What's astonishing is what new and surprising things can turn up unexpectedly," she says. Amine oxidase enzymes offer a striking illustration.

These common mammalian enzymes help control the body's levels of amines, a class of compounds that includes hormones and neurotransmitters. Until the 1980s, amine-oxidase aficionados believed that an old standby – vitamin B6 – collaborated with these enzymes. But researchers could produce only indirect evidence for vitamin B6's involvement, leading some to suspect a different – and perhaps yet undiscovered – sidekick, Klinman says.

In 1984, an intriguing candidate sidled into view. Studying a bovine amine oxidase, two independent research groups found clues that pyrroloquinoline quinone (PQQ) might be the enzyme's missing sidekick in cows – and perhaps in humans as well, Klinman says. That still would not make PQQ a vitamin – unless researchers could show that the body had to obtain it from outside sources.

The PQQ findings thrilled enzymologists because they helped account for many confusing amine-oxidase characteristics. For instance, these enzymes participate in the transfer of electrons between several different compounds. So does PQQ. The question was: Do they do it as a team?

"It just seemed to make a lot of sense," Klinman recalls. And sure enough, over the following six years, at least 10 studies uncovered additional hints for PQQ's role as the enzymes' necessary partner.

But as Klinman points out, "Just because something makes sense doesn't mean it's right."

The first crack in the scaffold of evidence for PQQ emerged in a report in the May 25, 1990 SCIENCE. Using methods that incontrovertibly identified the cow enzyme's elusive helper, Klinman and her colleagues determined that it was not PQQ but a related quinone called 6-hydroxydopa (TOPA).

"A quinone explained many of the properties of these enzymes," she says. "It's just that PQQ is the wrong quinone."

An even greater surprise awaited the researchers: The newly identified helper did not resemble the standard coenzymatic vitamins, which float around in a cell until nabbed by an enzyme in need. Instead, TOPA turned out to be a built-in partner, which the cell fashions (after the amine oxidase is made) by modifying one of the enzyme's component amino acids.

Having never seen such a built-in helper in mammals, "we were just blown away," Klinman recalls. Although TOPA is not a vitamin – because it's made by the body's own cells – it combines the chemical talents of vitamin B6 and vitamin C, a "curious" property necessary to the functioning of this enzyme, Klinman says.

Since the discovery of TOPA in cows, researchers have come to believe that most of the enzymes previously thought to collaborate with PQQ instead team up with either conventional helper molecules or TOPA-style built-in partners.

While TOPA has no prospects of being named a vitamin, PQQ's status remains unresolved, asserts Robert B. Rucker of the University of California, Davis.

For one thing, Rucker says, if PQQ is not a vitamin, why do his studies consistently show that young mice become sickly when their diets lack the chemical? In 1989, he published findings suggesting that immature animals, at least, must obtain PQQ from outside sources.

PQQ's elusive nature may account for some of the confusion over its role, says Paul M. Gallop of Children's Hospital in Boston. Until recently, detecting PQQ in the body was a tedious task. In the January 15 JOURNAL of BIOLOGICAL CHEMISTRY, however, Gallop and his colleagues describe a more reliable method, which they have begun to use in a series of new experiments.

One of those experiments will test whether PQQ helps control brain levels of dopamine, a neurotransmitter depleted in people with Parkinson's disease. The group's preliminary results show PQQ in human body fluids such as breast milk, blood and cerebrospinal fluid.

"If it's there, then it's probably serving some function," Rucker says.

Is it a true vitamin? Maybe yes, maybe no. But as new clues emerge from these and other investigations, PQQ may finally gain a label that sticks. □

What is a vitamin?

Vitamins are vital nutrients that the body cannot produce on its own. Even minute deficiencies of these compounds produce characteristic disorders.

Too little vitamin B1, or thiamine, for example, leads to beriberi, causing pain in the limbs and distorted skin sensations. Insufficient ascorbic acid, or vitamin C, produces the skin sores and rotting gums characteristic of scurvy.

Physicians identified vitamin deficiencies as early as 1747, but the term "vitamine" – later vitamin – wasn't coined until 1912. Chemists identified the first member of this class, vitamin A, in 1930. Cobalamin, or B12 – the thirteenth and most recently discovered vitamin – was identified in 1948.

Before a compound can achieve vitamin status, studies need to show that higher animals, such as mice, must obtain the essential substance either from the diet or from bacteria living in the gut. Researchers test for this by providing the animals a diet free of the candidate vitamin and administering antibiotics to kill off intestinal microbes. *– W. Gibbons*