An enzyme for urea reveals its structure

After more than half a century, scientists have finally pinned down the molecular structure of the enzyme urease.

Many bacteria, fungi, and plants — but not animals — use urease to break up molecules of urea, commonly found in urine and biological waste, releasing nitrogen-containing compounds. "This finding has agricultural relevance," says P. Andrew Karplus, a biochemist at Cornell University. "Much of the nitrogen in fertilizer comes from urea, which bacteria degrade into ammonia and CO_2 using urease."

Knowing the enzyme's structure may make it possible to synthesize urease inhibitors to control the rate of nitrogen release. "That could improve fertilizers," says Karplus, who, along with Cornell chemist Evelyn Jabri and their colleagues, describes the structure in the May 19 SCIENCE.

Some urease-secreting bacteria can also infect people. These bacteria seek out the human excretory system, where they thrive and inflame tissues in the urinary tract, kidneys, and stomach. Researchers find these bacteria associated with ulcers, gout, and gallstones, Karplus observes.

"The enzyme's structure is important biomedically because urease inhibitors may be able to stop these invasive bacteria," he says. A potent inhibitor might yield better drugs for treating ulcers or urinary tract infections.

Triggering antibodies to urease might prevent infection, he observes. "Some groups are already looking at possible urease-based vaccines for immunizing people against these bacteria."

Urease has "a long and distinguished history," says Stephen J. Lippard, a chemist at the Massachusetts Institute of Technology. In 1926, urease from jack beans became the first enzyme crystallized in the laboratory. "This accomplishment afforded incontrovertible proof that enzymes were well-defined chemical compounds," Lippard says.

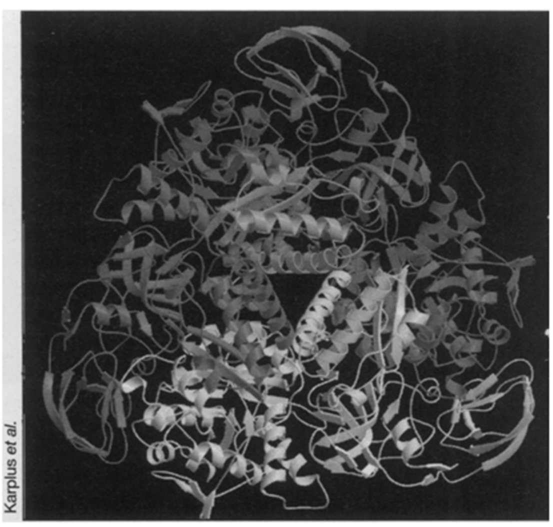
An unusual feature of urease is its dependence on nickel to grab onto and break up urea in the enzyme's active site, Karplus points out. Most similar enzymes rely on zinc to do their handiwork.

Karplus' group isolated urease from the bacterium *Klebsiella aerogenes*. Using X-ray diffraction, they resolved the enzyme's molecular architecture down to a scale of 2 nanometers. "This fascinating structure," says Lippard, "reveals the intimate details of the molecular geometry at the active site."

With this crystal structure in hand, "an important chapter has ended in the history of enzymology," says Lippard. "For the field of bioinorganic chemistry, however, the structure helps to open new frontiers, one of which is to understand the principles by which [the active site] functions."

Another matter to discern, says Lippard, lies in nickel's various roles in biology. Given that urease appears to be the only enzyme of its type to use nickel, the metal ion's distinctive action remains intriguing, though "uncertain."

Still, observes Lippard, "the crystal structure has clearly revealed the players on the catalytic stage." — *R. Lipkin*



Karplus *et al.*

The structure of the enzyme urease.

Smoking depletes vitamin C from mom, fetus

In his later years, Nobel laureate Linus Pauling touted megadoses of vitamin C as a preventive medicine. He speculated that the vitamin prevents diseases ranging from the common cold to cancer. While conventional nutritional wisdom questions the benefits of such a regimen for everyone, new evidence suggests that pregnant smokers may do well to double their vitamin C intake.

A research team from Our Lady of Mercy Medical Center in New York followed a group of smoking and nonsmoking women through their pregnancies and reported its findings last week in San Francisco at the annual meeting of the American College of Obstetricians and Gynecologists.

The team found not only that the 226 smoking mothers had lower concentrations of vitamin C in their bloodstreams compared to the 174 nonsmoking participants, but that their fetuses got comparatively less vitamin C — even when both groups of women had the same vitamin C concentrations.

"It really appears that the smokers may need more vitamin C and maybe more of other nutrients that we haven't identified yet to get the appropriate amount of nutrients across the placenta to the fetus," says study collaborator Lois Brustman.

Previous work had established that in order to neutralize the damaging free radicals found in tobacco smoke, smokers in general use more vitamin C than nonsmokers. In fact, the National Research Council included two-thirds more vitamin C for smokers in its 1989 Recommended Daily Allowance guidelines. However, the guidelines didn't address the needs of pregnant smokers.

The New York team followed the 400 women through their pregnancies and found striking differences in the amount of vitamin C in their bloodstreams. On average, the smokers had 15 percent less vitamin C than the nonsmokers.

Surprisingly, the smokers' bodies appeared to notice the deficit: Smokers consumed 30 percent more vitamin C. Team leader Kevin D. Reilly says the smoking mothers "appeared to be satisfying a biological craving to consume vitamin C–containing foods and juices," because the smokers didn't know that smoking specifically depletes vitamin C.

Because vitamin C needs increase substantially in pregnancy, Reilly's group speculated that the discrepancy between the amount of vitamin C consumed by pregnant smokers and the amount in their blood may result from the dual stresses of smoking and pregnancy.

Typically, newborns have twice the vitamin C concentration of their mothers. The New York team examined the concentrations of vitamin C in the mothers' bloodstreams and in blood from the infants' umbilical cords. While the newborns of nonsmoking mothers had twice as much vitamin C in their cord blood, the newborns of smokers had only 1.5 times as much as their mothers.

"This isn't just a case of less available vitamin C. We are looking at a potential problem with transport of vitamin C across the placenta," Brustman says. This, she adds, indicates that smoking mothers may need twice as much vitamin C as nonsmokers.

While the study is only preliminary, biochemist Balz Frei of Boston University Medical Center calls the finding "interesting" and "indicative of a transport problem, since the ratio between mother and infant is different."

Another result indicates problems with the placentas of smoking mothers. When the researchers looked at the three stages of labor, they discovered that the final stage, when the uterus expels the placenta, lasted nearly twice as long for the smokers. "This can be particularly dangerous, because the longer stage 3 is, the more a woman is likely to hemorrhage," Reilly says.

The team plans to study whether low vitamin C, which plays a role in connective tissue development, prolongs the final stage of labor. — *L. Seachrist*