'70s date back 300,000 years. Omoto says that Serizawa's stature and his role as mentor to Hiroshi Kajiwara, an archaeologist at Tohoku Fukushi University and deputy director of the Tohoku institute, tended to deflect criticism of the Tohoku group's findings.

Serizawa says that he made no attempt to shield the group from criticism. In fact, he says he also had questions about the dating of the artifacts, which he recently published in *Chuo Koron*, a leading intellectual magazine. But he didn't express his reservations earlier, either to the group or in public, because "they said there was no mistaking the old strata that yielded the artifacts."

Fujimura emerged from seclusion on 18 December to reiterate his claim that he had planted findings at only the Kamitakamori and Hokkaido sites. But Kajiwara agrees that a large cloud now hangs over all of Fujimura's work, which involves 33 excavations directly and extends to 160 other efforts. Nevertheless, Kajiwara says, "I still have confidence that we are working with Paleolithic sites." Peter Bleed, a professor of anthropology at the University of Nebraska, Lincoln, who just completed a 6-month stint as a guest professor at Tohoku University Museum, agrees. "It would be a real tragedy if researchers elsewhere concluded that none of the early Paleolithic evidence coming out of Japan could be trusted," he says.

There is also no consensus on how to correct the deeper problems that may have contributed to the fraud. Serizawa blames it on Fujimura's popularity with the media and a lack of analysis. "From the 1950s through the 1970s, we never had these problems, and I have confidence in the work done in those years," he says. "The problems started in the 1980s, and they can be resolved by investigating the artifacts Fujimura was involved with," he adds. Kajiwara predicts that "there will be a change in how these press conferences are arranged."

But many think the problem runs deeper. Ken Amakasu, professor emeritus of Niigata University and chairman of the Japanese Archaeological Association, says, "It is clear that more time should be spent on analysis before making claims." Greater collaboration with foreign scientists would raise standards of scholarship and introduce the notion of free-wheeling scientific debate, Omoto believes, although Keally warns that their impact would be lessened by language and cultural barriers.

Takeoka isn't sure what will happen, but he's hopeful that his colleagues will learn from Fujimura's misconduct. "I do think researchers are reflecting on various aspects of this incident," he says. "If this leads to even a little improvement in the current state of affairs, I'll be really happy."

–DENNIS NORMILE

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PHARMACOLOGY

How the Body's 'Garbage Disposal' May Inactivate Drugs

A protein sentry that triggers the liver's defense against chemical toxins can explain drug interactions—and an old legend

Some 2000 years ago, King Mithridates of Pontus, a region on the Black Sea that is now part of Turkey, performed an astonishing trick. According to a legend immortalized in an A. E. Housman poem, the ambitious and warring monarch feared his enemies would poison him. To guard against this, he dosed himself with small amounts of poisons to build up his immunity. The technique worked: Mithridates survived the assassination attempt he predicted, and his name came to mean an antidote for poison.

Molecular endocrinologist Ronald Evans now thinks he has a molecular explanation for Mithridates's invulnerability. Recent work by Evans at the Salk Institute for Biological Studies in La Jolla, California, and by other teams around the world is revealing the machinery of the body's defense against poisons and other foreign chemicals. The work, reported over the last year, helps explain not only an ancient riddle but also why taking certain drugs or herbs, like the popular St. John's wort, can render others ineffective.

Interference. St. John's wort (*Hypericum perforatum*) triggers the body's defense against chemical toxins—and renders many other drugs impotent.

Scientists have known for years that the body has a chemical surveillance system in the liver. Sensing the presence of potentially dangerous chemicals, the liver cells crank up the production of an enzyme called CYP3A, which breaks down a host of compounds, including many toxins. "CYP3A is like the liver's garbage disposal," says Steven Kliewer, an endocrinologist at GlaxoSmithKline in Research Triangle Park, North Carolina.

Many scientists suspect that this "garbage disposal" evolved to fend off the countless toxins to which animals are exposed in the environment, including the poisons plants produce to avoid being eaten. But exactly how it works has long been a mystery. A key question is what receptors in the liver cell initially sense the toxin and alert the chemical police to seek and destroy it. Most scientists expected to find a suite of receptors, all tailored to recognize specific threats. But over the past few months, converging research by several teams suggests that just one protein—perhaps aided by a handful of assistants—can recognize the thousands or even tens of thousands of potentially harmful compounds present in the environment and prompt the liver to mount an all-out attack on them.

One set of clues came from an unexpected line of research: Patients taking St. John's wort, a popular herbal remedy for depression. In late 1999 and early 2000, several papers reported that in some half-dozen patients taking St. John's wort, the blood concentrations of other drugs they were taking—including the asthma drug theophylline and the anticlotting drug warfarin—were dramatically reduced. Several women taking birth control pills reported breakthrough bleeding, suggesting that the pill's hormone levels had dropped. In another well-publicized example, two heart transplant recipients in Germany experienced life-threatening transplant rejections a few weeks after starting to take St. John's wort. Their physicians found that levels of the immunosuppressant cyclosporin had plummeted to half the normal dose (see sidebar).

Many scientists suspected that St. John's wort was activating the CYP3A pathway, which would accelerate the breakdown of the other drugs. Intrigued, Kliewer and his Glaxo colleagues decided to test whether St. John's wort was working through the PXR receptor, a protein they had discovered in mice several years earlier and had been

A Worrisome Side Effect of an Antianxiety Remedy

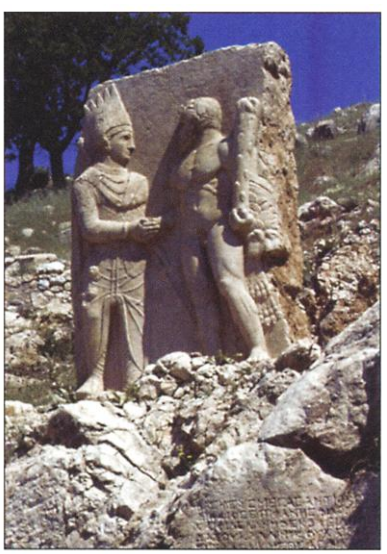
As reports came in on drug interactions with St. John's wort, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) went on alert. In February, NIH scientists reported in *The Lancet* that, in healthy volunteers, St. John's wort cut in half the blood levels of the antiretroviral drug idinavir commonly used to treat HIV infections. In the same issue, German doctors reported that St. John's wort had caused levels of an immunosuppressant drug to plummet in two heart transplant recipients. That week, the FDA issued an official warning to doctors and pharmacists noting that the herb could interfere with dozens of drugs, including the antiseizure medication phenobarbital, the breast cancer drug tamoxifen, the oral contraceptive ethinyl estradiol, and antiretrovirals used to treat AIDS.

As scientists discovered a few months later, St. John's wort triggers production of an enzyme called CYP3A, which breaks down potential toxins in the liver. In addition to warding off poisons, the CYP3A system also helps to metabolize hormones such as estrogen, testosterone, and their precursors. For that reason, the FDA now warns that women taking birth control pills should not take St. John's wort, because CYP3A breaks down the synthetic hormones designed to prevent pregnancy. No one has done a systematic study of the pill's failure rate in women taking the herb, says complementary medicine specialist Edzard Ernst of the University of Exeter in England, but "there could be a few 'St. Johns' walking the street now."

The work has uncovered an unexpected potential benefit as well. The latest work by teams led by Steven Kliewer at GlaxoSmithKline in Research Triangle Park, North Carolina, and Ronald Evans at the Salk Institute for Biological Studies in La Jolla, California—which they have described at several meetings—shows that the CYP3A system also helps break down bile acids. Kliewer believes that St. John's wort might be useful in alleviating an especially difficult-to-treat condition called cholestasis, which occurs when people can't break down bile acids properly and toxic byproducts build up in the liver. "There are anecdotal reports that St. John's wort is useful for treating liver diseases," Kliewer says. He suspects these reports might come from cholestasis patients whose CYP3A production has been boosted. **–G.V.**

intensely studying ever since. Evans and his colleagues knew that PXR, which has a human counterpart known as SXR, triggered production of CYP3A. But they did not know what activated PXR in the first place.

GlaxoSmithKline scientist Linda Moore headed off to the local pharmacy, where she bought three preparations of St. John's wort. When she tested their effect on the PXR receptor, she hit paydirt. "We found that it was extremely efficient at activating PXR," says Kliewer. "Rarely in science do things work the first time, but this was really dramatic." The team tested several active components of St. John's wort and found that almost all the PXR activity was caused by a molecule called hyperforin—the same compound that many scientists think bestows St. John's wort's antidepressant activity. St. John's wort, it seems, triggers PXR, which cranks up production of the CYP3A enzyme, which in turn breaks down cyclosporin, idinavir, and a host of other drugs.



Invincible. King Mithridates of Pontus (left, pictured with Hercules) may have escaped assassination attempts by priming his CYP3A enzyme, giving him tolerance to poisons.

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What's more, says Evans, PXR seems to be almost solely responsible for activating the chemical police system. His evidence comes from experiments with knockout mice done to further characterize PXR. In July, Evans and his colleagues reported that mice lacking the *PXR* gene did not respond to compounds that typically kick off the CYP3A system in mice. But when the researchers knocked out *PXR* and inserted *SXR*, the animals had a "humanized" CYP3A response: They still failed to respond to classic triggers of the mouse CYP3A system, but they reacted strongly to at least a dozen compounds that activate the human system, including the antibiotic rifampicin—notorious for triggering drug interactions. Because switching a single gene caused such a dramatic change, Evans argues that *PXR* and *SXR* are the primary sentries for the CYP3A system. The overall system "is a lot simpler than we thought," Evans says.

There is evidence that *SXR* does not work entirely alone, however. In October, a team led by David Moore at Baylor College of Medicine in Houston, Texas, reported in *Nature* that another gene called *CAR* seems to play a similar role, activating an enzyme called CYP2B in response to phenobarbital. CYP2B, in turn, breaks down a number of compounds, including cocaine. But it seems to have a narrower scope than *SXR* does, Kliewer says.

No one yet understands how *SXR* and *PXR* can respond to so many different chemicals. Kliewer suspects that the receptor may have an especially large binding site, which can accommodate a variety of molecules. To test that theory, scientists must obtain the crystal structures of the receptor with many different ligands—a daunting project that several teams are working on, says Kliewer. He expects an answer in the coming year.

No matter how the receptor works, Evans predicts that his humanized mouse model will be a boon to pharmaceutical companies. By testing compounds in these knockout mice, companies can determine which ones activate the CYP3A system and thus potentially interfere with other medications. Companies today use cultured human cells to test for a range of *CYP* gene activation, but Evans says such tests are more variable than a humanized mouse might be.

Others are not convinced. The mouse model is "a great first step," says Mitch Lazar of the University of Pennsylvania School of Medicine, but he expects that research will uncover additional receptors, such as the *CAR* gene, that play an important role in drug interactions.

However many receptors are involved, the defense system worked for Mithridates—if the legend can be believed. Evans theorizes that the small doses of poison Mithridates ingested primed his SXR receptor. With the CYP3A system on high alert, Evans says, otherwise deadly doses were easily neutralized. As A. E. Housman describes it:

They put arsenic in his meat
And stared aghast to watch him eat;
They poured strychnine in his cup
And shook to see him drink it up:
They shook, they stared as white's their shirt:
Them it was their poison hurt.
—I tell the tale that I heard told.
Mithridates, he died old.

–GRETCHEN VOGEL