Inherit the Weeds

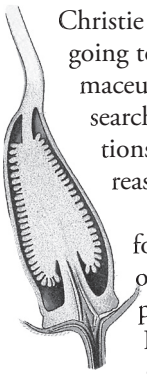
A search for the pharmaceutical experiment station traces the evolution of the drug industry. But where have all the flowers gone?

Reprinted from *On Wisconsin Magazine*, Winter 2007

By John Allen

Mystery novelists are going to love Jon Thorson.

That was the first thing I thought when I heard about his discovery — every devotee of Arthur Conan Doyle and Agatha Christie and Raymond Chandler is going to love this professor of pharmaceutical studies. Through his research to find new cancer medications, he's giving the world a new reason to look at digitalis.



Digitalis is a plant — the foxglove — and it's poisonous. It was reputedly the poison of choice of Lucrezia Borgia back in the Renaissance — legend says she kept a supply, dried and powdered, in a hollowed-out ring. Then, when one of her politically convenient lovers became inconvenient, she'd pop open the ring, plop the stuff in his drink, and soon he was conveniently dead. Digitalis can cause heart disturbances, delirium, convulsions, vomiting, anorexia, diarrhea, hallucinations, and all manner of yuck.

But digitalis is also a medicine. For centuries, people have used it in traditional remedies for congestive heart failure. It's a beautiful flower that can either cure or destroy the heart — which is handy when one wants to be symbolic. You can see why it's perfect for whodunits.

But I was preoccupied with a more current mystery. Once upon a time, I knew, the UW had the nation's best medicinal garden, called the pharmaceutical experiment station. I'd read, however, that it had disappeared decades ago. If Thorson was working with digitalis, where did he get his foxglove flowers?

I went to Thorson's lab, but unfortunately, he didn't have any foxglove. His office and lab are in the UW's new Rennebohm Hall, six stories above the soil and all that grows in it. He's no gardener. And anyway, he doesn't really work with digitalis, but with digitoxin, one of the active ingredients in the plant. He's one of several pharmacy school researchers who are looking into drugs developed from natural substances, as opposed to those created through laboratory synthesis, with a goal of turning them into something entirely new.

What Thorson and his lab have done is invent a process called glycorandomization, in which they take a naturally occurring chemical (digitoxin being one of them) and then make it unnatural. They add and subtract sugars to it to change the way it reacts with other molecules and with cells.

This is important because digitoxin doesn't just aid the heart — it also seems to combat some forms of cancer, including those of the breast and colon. Cancer patients who are also taking digitoxin for a heart problem see a reduction in tumor size, which is good. What's bad, though, is that cancer patients who don't have a heart condition can't really take digitoxin — it has that poisonous effect that Lucrezia Borgia found so entertaining.

"What we wanted to do," says Thorson, "was allow the digitoxin to attack the tumor without having any effect on the patient's heart."

Glycorandomization seems to do that. When Thorson's lab put digitoxin through this process, he could make analogs of the chemical that seemed to attack tumor cells but not heart cells.

So, neat: cancer is cured, right?

Not so fast. Thorson's experiments had only been done in vitro — that is, in test tubes and Petri dishes and such. This is good enough for an article in the Proceedings of the National Academy of Sciences and a press release, but it's not really good enough to convince the Food and Drug Administration to approve the new chemical for use on people. First it'll have to go through animal testing, and if it does well there, then clinical trials on human beings will follow. It's a long process — on average, it takes twelve years between when a novel drug is discovered and when the FDA grants approval.

"Right now," said Thorson when I visited him in June, "our digitoxin derivative is at the pharmaceutical experiment station. They've got to prepare it for the next stage."

The pharmaceutical experiment station, it turns out, isn't gone at all. But what did this one-time bastion of natural drugs — that giant medicinal garden — have to do with Thorson's unnatural experiments? This, I figured, was worth checking out. So I went to the spot where it all began — the triangular lot between Monroe Street and Breese Terrace, just south of Camp Randall Stadium.

But the station wasn't there.

It's easy to spot the pharmaceutical experiment station's first home, because standing there is a monument to something else. A vaguely obelisk-shaped pile of footballs gives testament to the Badgers' recent glory. The entire lot is now covered in athletic sprawl — the Field House, parking lots, that sculpture.

But in the summer of 1913, it was covered in row upon row of medicinal plants: several species of digitalis; Cannabis indica, used in the production of marijuana and hashish (which, I'm told, is still grown in various places on campus); belladonna, which produces atropine, an eye dilator, decongestant, and poison antidote; yarrow, an astringent; boneset, which can treat fever; as well as cardamom, catnip, peppermint, and many others. These would have been tended by scientists and graduate students, and at the center of them all was Edward Kremers 1888.

Kremers was the dominant force behind the pharmaceutical experiment station. As the head of the UW's pharmacy program from 1893 to 1933, he virtually created the modern study of drugs in Wisconsin. Though he worked almost exclusively with plant-based medicines, he was, like Thorson, no traditional herbalist. In

fact, he seems to have despised such practitioners. The major theme of his career was the effort to make the pharmaceutical world — both in study and industry — more rigorously scientific. In 1893, he created the nation's first bachelor's degree program in pharmacy (previously, the UW had granted a two- or three-year diploma), and followed shortly after with the first master's and doctoral programs.

When he looked at the lack of quality control among his commercial colleagues, he did not conceal his disgust. "Most crude drugs are very crude indeed," he wrote. "No one would be content to use wild cereals for food purposes, yet we are not only content to receive our drugs from nature as she chooses to supply them, but we allow some of the most ignorant members of human society to spoil, in no small measure, what nature happens to provide."

He conceived of the pharmaceutical experiment station as a way to produce high-quality medicinal plants through a scientifically controlled process. But it was also an opportunity to change America's drug economy and place Wisconsin at the center of a lucrative industry. In the same way that the UW's agricultural experiment station was revolutionizing farming, he reasoned, a pharmaceutical station could revolutionize drug production.

Consider thymol, an antiseptic produced from thyme. America's pharmacies imported their supply of the drug from companies based in Germany, where it was manufactured from plants grown in India.

"While we have been importing about ten thousand pounds of thymol annually," Kremers wrote, "a weed growing on the sandy areas along the lower course of the Wisconsin River has probably been producing enough thymol to have supplied the United States."

Kremers lobbied state legislators to fund his station, and in 1913, they came through, passing Bill Number 247S, which gave him $2,500 a year to establish and maintain his medicinal garden, which he sited near Camp Randall.

This was his great contribution to the Wisconsin Idea. Not only did he work to perfect the science of drug farming, but he also published circulars for the education of working pharmacists. As for the surplus plants, the ones the UW didn't need for research or teaching, Kremers shared them with druggists around the state.

The project began paying dividends within a year, when World War I broke out. The two most important pharmaceutical exporting nations were Britain and Germany, and when both turned their economies over to war production, America discovered a need to develop a domestic drug industry in a hurry. The only place conducting research in this field was Kremers' station.

Letters poured in from farmers, pharmacists, and even the Ladies' Home Journal, asking Kremers how to create a commercially viable medicinal garden. The U.S. Department of Agriculture's Bureau of Plant Industry recommended that every state in the nation set up a facility like the UW's.

In four decades of heading the UW's pharmacy program, Edward Kremers virtually created drug study in Wisconsin. His innovations include not only the experiment station, but also the nation's first undergraduate and graduate pharmaceutical degree programs.

And this, essentially, is why it had to leave Camp Randall. As Kremers's pet project became more successful, the university decided that it needed more room. The state doubled the station's budget in 1917, and the UW moved it out to Eagle Heights.

But you won't find it there, either.

There are gardens at Eagle Heights, naturally, and some of them contain medicinal plants. But the Eagle Heights Community Gardens aren't in any way related to the pharmaceutical experiment station. They're not even in the right spot. The station's home now lies beneath the 100 block of the Eagle Heights Apartments.

When it moved there, the station was at the height of its influence. It was lauded in Science; Germany's Pharmazeutische Zeitung cited its "many experiences of scientific accuracy"; and even the London Daily Telegraph mentioned that Britain's chemists looked on the UW's station with a touch of envy.

But scientific advances were beginning to change the pharmaceutical industry. In 1909, in a lab in Germany, bacteriologists Sahachiro Hata and Paul Ehrlich identified Salvarsan, the first true antibiotic, and in the decades that followed, drugs produced by laboratory synthesis began to show far greater promise than those refined from naturally occurring substances.

"Ehrlich's discovery of Salvorsan was really the first specific chemical drug," says Glenn Sonnedecker MS, PhD, the former head of the American Institute for the History of Pharmacy. "And then there were the sulfonamides and penicillin. In a short period after Ehrlich's breakthrough, there was a major shift in drug therapy."

This shift, combined with a tightening state budget during the Great Depression, spelled the end for the pharmaceutical experiment station. The legislature cut its funding in 1933, and when Kremers retired shortly afterward, interest in the station died out completely.

But curiously, though the state cut its funding, it didn't remove the statute that originally established the station. So for the next seven decades, it existed as a sort of bureaucratic fossil, waiting to be exhumed. That's exactly what the School

of Pharmacy did in 2003 — but naturally, the station today is not quite the one Kremers had planned.

I finally found the pharmaceutical experiment station at its third home, on the second floor of Rennebohm Hall, on the west side of campus near the hospital. It's now called the Lenor Zeeh Pharmaceutical Experiment Station, after former Rennebohm Drug Company vice president Lenor Zeeh '36, whose donation helped dig it out of obscurity. I suppose you could say its roots reach to Kremers's old station, but only metaphorically, as it now has no roots — or flowers, leaves, or seeds, for that matter.

Nevertheless, says the Zeeh Station's first director, Lynn Van Campen MS, PhD, "when we created this facility, we were very careful to keep pharmaceutical experiment station in the name." One reason the school insisted on this, Van Campen says, was legal — since the legislature had never removed the statute that created the station, it couldn't object to having it up and running again.

But more importantly, there's symbolism. Today's station may not perform the same work as Kremers's old project, but it hopes to fill the same purpose: to improve the UW's pharmaceutical research and aid the drug industry. Where the problems Kremers hoped to solve revolved around consistency and quality, the problems today are cost and time. "The mission is essentially the same," says Van Campen. "We've just updated it a little."

Pharmaceuticals still offer huge economic possibilities. According to the consulting firm IMS, global drug sales added up to $643 billion in 2006, nearly double the sales mark from 1999. And the UW is hoping for a piece of that action. The Wisconsin Alumni Research Foundation, which acquires patents for inventions from UW-Madison researchers, lists more than 300 new patents or patent applications under the category of pharmaceuticals, and 197 under drug discovery.

But taking new drugs from discovery to market is a long, risky, and expensive process. According to another consultancy, Bain and Company, it costs upwards of $1.7 billion for a newly discovered chemical to move through animal testing and human clinical trials to FDA approval.

The Zeeh Station aims to help in between those stages. For instance, it had no role in the development of Thorson's glycorandomization technology — the work of invention and discovery was done in Thorson's lab, and the compounds it produced passed only briefly through the station on their way to further study elsewhere.

What the Zeeh Station does is called formulation — that is, turning laboratory chemicals into actual drugs. This means its staff has to figure out the new chemical's physical structure. (Is it crystalline or amorphous? Does it have multiple crystalline structures?) It has to determine whether the stuff will dissolve (and if so, in any substance that won't either render the chemical impotent or, worse, poisonous), and find a way to keep it stable. They also have to find the best delivery system for the drug candidate — as an injection, for instance, or a pill, capsule, salve, or slurry.

According to emeritus pharmacy professor Kenneth Connors MS, PhD, getting potential new drugs through the formulation stage is one of the obstacles between pharmaceutical research and the marketplace. "There was this gap in drug development resources," he says. "When new compounds were discovered, they weren't really far enough along [for pharmaceutical companies to take a chance on funding further research], because these intermediate stages hadn't been performed."

And drug companies want to be careful about what research they fund, because the odds are against them. For every five thousand newly discovered chemical compounds with drug potential, only five are ever approved for testing on humans, and only a fifth of those ever earn FDA approval, meaning that 99.98 percent of all drug candidates never see any return on the research investment. By helping to develop drugs beyond initial discovery and prepare them for a possible future, the Zeeh Station aims to give both scientists and pharmaceutical companies a boost. Van Campen, who spent several years working for the international pharmaceutical firms Boehringer Ingelheim and Nektar before returning to the UW, says her former colleagues were thrilled to hear that the station "speaks development," preparing new compounds for the practical problems they'll face through the approval process. It should, she hopes, give a better idea of what will and won't succeed.

"There's a saying in big pharma," says Van Campen. "If you're going to fail, fail fast. It's a lot less expensive."

That's the role of today's pharmaceutical experiment station — to help potential drugs fail faster so that only the best candidates will move forward, giving scientists (and the companies that invest in them) a better idea of which projects to pursue. As the station's scientific director, Mark Sacchetti MS, PhD, points out, it's still gardening — just of a different sort.

"We work with researchers and companies to find the best molecules to take forward," he says. "Our job is essentially weeding out the aspiring drugs that won't work." ●

John Allen is senior editor of *On Wisconsin*.

Announcements

Tom Woller, a 12-year Aurora Health Care veteran, has been named vice president, pharmacy services. Woller previously served as regional director, pharmacy services, Metro Region. He joined the organization in 1995 as director, department of pharmaceutical services, Aurora St. Luke's Medical Center.

Aurora's inpatient hospital and Aurora Visiting Nurse Association pharmacy operations are transitioning from a regional to a centralized, system-wide structure, under Tom Woller, newly named vice president, pharmacy services. The new Department of Pharmaceutical Service will allow all Aurora hospital pharmacies to implement similar services, share clinical resources, and establish best practices across the system. These changes will not apply to Aurora's retail pharmacy operations. ●