Profile of V. Craig Jordan

In the mid-1970s, breast cancer survival rates were dismal. Researchers hoped to find a drug capable of thwarting the disease, but the prospects were few and far between. In a laboratory on the campus of the Worcester Foundation for Experimental Biology in Shrewsbury, Massachusetts, a group of experimental rats were dying from breast cancer. A researcher gave them a triphenyl ethylene—a purported antiestrogen—with the slim hope that it would slow progression of the disease. The cancer disappeared (1). Within a few years, a clinical trial of the drug was launched among women suffering from breast cancer. The women’s tumors, just as those in the rats, shrank. By 1978, the US Food and Drug Administration had approved a triphenyl ethylene-based drug known as tamoxifen for the treatment of late-stage breast cancer (2).

Today, tamoxifen is a resounding success. By the numbers, breast cancer mortality rates held steady from 1975 to 1990 but declined by almost 20% from 1990 to 2000. Two-thirds of that decline is attributable to adding tamoxifen to the chemotherapy regimen already used to treat breast cancer. Among breast cancer survivors taking tamoxifen for 5 years, the standard dosage for the drug, mortality declined by nearly 40% (3, 4). The researcher who cured the rats, V. Craig Jordan, is now known as the “Father of Tamoxifen.”

Since discovering tamoxifen’s potential to prevent breast cancer more than three decades ago, Jordan, a 2009 inductee to the National Academy of Sciences, has devoted his career to understanding the characteristics of the drug—its benefits, pitfalls, and other applications. Thanks to that work, it is now known that tamoxifen and similar drugs act as both estrogen inhibitors and estrogens, depending on where they travel inside the body. Collectively, the drugs are referred to as selective estrogen receptor modulators, or SERMs. SERMs are now routinely prescribed to treat not just breast cancer but other estrogenic disorders, such as osteoporosis. Jordan says there is hope of someday using this same class of drugs to reduce the devastation of coronary heart disease.

In his Inaugural Article, Jordan returns to the topic of breast cancer to explain a paradox in the literature that has plagued scientists for decades. From his own work, Jordan knew that tamoxifen’s antiestrogenic properties stopped the growth of breast cancer. However, in the 1940s, another researcher by the name of Alexander Haddow showed that giving postmenopausal women estrogen also caused the disease to grind to a halt (5). Now Jordan has explained how estrogen can both promote and prevent breast cancer. “We have solved a 70-year mystery,” he says (6).

Early Childhood

Jordan, the Alfred G. Knudson Jr. Chair in Cancer Research at the Fox Chase Cancer Center in Philadelphia, Pennsylvania, was born in New Braunfels, Texas, in 1947 but moved to the United Kingdom as an infant with his British parents. Growing up, Jordan developed a deep, almost singular, infatuation with chemistry—the origins of which he cannot recall. At age 13, his mother let him build a chemistry laboratory in his bedroom, a prescient if costly decision.

“There were always fires in the bedroom and bombs going off in the back of the garden,” Jordan says, recounting an experiment with sodium chloride that went horribly awry. Rather than blow up the house, Jordan chuckled the whole, smoldering mess out the window—creating a crater-sized gap where grass once grew. “My parents were furious,” Jordan says. “Telling them not to worry, Jordan re-seeded the lawn and added some copper sulfate to expedite the growing process.”

However, where Jordan excelled in chemistry, he floundered in other “lesser” subjects. “I thought plants were stupid,” he says. By age 16, when he needed to pass five subject examinations to continue his education, Jordan only passed three, forcing his mother to beg the headmaster to let him retake the tests in a few months. Luckily, he passed.

By then, Jordan had become a tutor to his peers, teaching them the basics of chemistry, pharmacology, and biochemistry. Seeing that talent, a teacher by the name of Charles Bescoby convinced Jordan and his parents that he should not go to work as a technician at nearby Imperial Chemical Industries (ICI) Pharmaceuticals as he had long planned, but to university. Jordan received admission to the University of Leeds and graduated with a degree in pharmacology in 1969. He stayed on for another 3 years to receive his doctorate in the same subject, by then convinced that his future lay in developing a drug to treat cancer—a monumental chemistry challenge that appealed to Jordan’s intellect.

ICI 46,474

However, Jordan’s path to becoming a cancer drug expert was roundabout. At Leeds, he had extensively studied triphenyl ethylenes, the active compound in a drug that ICI had once believed would become the world’s first-ever “morning-after pill” (7).

Going by the code name ICI 46,474, the drug had been shown to block estrogen from reaching the uterus in rats. However, hopes were dashed when a clinical trial in humans found that more women got pregnant when taking the drug than not (8). Jordan was studying to see just how that drug worked in the body—a complex, voluminous project. When he went to defend his thesis in 1972, the university had no experts on staff capable of grasping Jordan’s thesis. So they called in Arthur Walpole, a researcher at ICI. Walpole held the patent on ICI 46,474 and was thus well placed to make sense of Jordan’s opus.

After that chance encounter, Walpole helped Jordan line up a postdoctoral fellowship at the Worcester Foundation for Experimental Biology. He was to work with endocrinologist Michael Harper to develop new contraception methods. By the time Jordan arrived in Massachusetts, though, Harper had accepted another job, and the Worcester Foundation told Jordan to set up his own laboratory for 2 years. “I was on my own,” Jordan says, with no idea of what to research. So he called Walpole, and the two men discussed turning ICI 46,474 into a drug to treat breast cancer.

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member’s Inaugural Article on page 18879.
Despite the failure of ICI 46,474 as a morning-after pill, Walpole and Jordan knew that the drug had antiestrogenic properties. Although breast cancer has different causes, for most women it arises when estrogen binds to receptor sites in breast cancer cells, allowing them to proliferate. A drug capable of binding to and inactivating those receptors might just thwart the spread of the disease, Walpole theorized. As a contraception researcher, Walpole had no opportunity to research that idea. So he handed the project over to Jordan.

In the early 1970s, Jordan induced rats to develop mammary (breast) cancer and confirmed that the tumors needed estrogen hormones to survive. When the rats were given ICI 46,474 the tumors shrank—a situation only mirrored in rats whose ovaries had been removed (1). ICI 46,474, he concluded, held promise as a drug to treat and prevent breast cancer in women with estrogen receptor sites in their breast cancer cells.

The idea that a drug could prevent breast cancer, however, remained controversial. Jordan’s paper was initially rejected before being accepted by the European Journal of Cancer Research in 1976. By then Jordan had completed his postdoctoral work in Massachusetts and become a full-time lecturer in pharmacology at his alma mater, the University of Leeds.

At Leeds, Jordan began studying how long tamoxifen should be administered in women with breast cancer. Using a rat tumor model, he showed that treatments shorter than a few years ultimately failed and the rats went on to develop tumors, whereas administering tamoxifen for longer periods thwarted the progression of the disease (9, 10). Today, the standard tamoxifen treatment extends over 5 years (11). Jordan’s research eventually prompted ICI to launch clinical trials into the use of tamoxifen as drug to treat breast cancer. “Tamoxifen slowly became hot,” Jordan says.

**Two Faces of Tamoxifen**

With tamoxifen poised for widespread rollout, however, Jordan began to worry that long-term estrogen deprivation through tamoxifen might trigger unforeseen side effects. Estrogen, he explains, is a double-edged sword for women. Although implicated in breast cancer, the hormone is also critical for the development of the cardiovascular system and bones. Jordan wondered whether long-term estrogen deprivation would lead to osteoporosis or heart disease. In 1980, he relocated to the University of Wisconsin, Madison, and started his own laboratory to research the health implications of using tamoxifen long term.

After finding that long-term tamoxifen use actually seemed to lessen the incidence of osteoporosis and heart disease in rodents (12), Jordan and colleagues launched a 2-year study of 140 postmenopausal women with a history of breast cancer. Half the women were treated with tamoxifen, whereas the other half received a placebo. As with the rodents, the researchers found that tamoxifen lowered cholesterol in women receiving the drug after 3 months and that such positive effects persisted for years (13). Similarly, bone density increased in women receiving tamoxifen but decreased in women receiving placebo (14).

Collectively, Jordan’s research suggested that tamoxifen and another related drug, raloxifene, were not antiestrogenic everywhere in the body as previously assumed, but were selective estrogens and antiestrogens (SERMs). “It turns out that different tissues interpret the drugs’ signal in different ways,” Jordan says. “So, paradoxically, tamoxifen and raloxifene built bones.”

Raloxifene is now widely prescribed to postmenopausal women in danger of developing osteoporosis (15). Estimates suggest that raloxifene use has inadvertently protected thousands of female users from developing breast cancer (16). The fact that women taking the drug report a lower incidence of breast cancer than the general population is just a “beneficial side effect,” Jordan says (17).

Not all side effects of SERMs were desirable, however. In 1988, Jordan, working with then graduate student Marco Gottardis, showed that tamoxifen promoted the growth of endometrial tumors in women (18). However, subsequent research made clear that the benefits of using tamoxifen for the treatment of breast cancer far outweighed the risk of developing endometrial cancer. Today, tamoxifen is estimated to save approximately 30 times more women than it harms (19).

Interestingly, raloxifene did not promote the development of endometrial cancer, suggesting that it may be preferable to tamoxifen. However, Cancer Prevention Results published a 2010 update of a five-year study comparing the long-term health outcomes of women receiving tamoxifen with women receiving raloxifene. Although participants in both groups had equal outcomes after 41 months of treatment, tamoxifen emerged as the more effective weapon against the recurrence of breast cancer when that time frame doubled. Specifically, raloxifene was shown to be less than 80% as effective as tamoxifen (20, 21).

**Estrogen as Cancer Killer**

Despite all his headway into revealing tamoxifen’s secrets, an issue that nig-
Living Legend

Growing up, Jordan says he did not have typical kid hobbies. Besides tinkering in his bedroom laboratory, he says, he loved ancient history. “I went on archaeological digs when I was a teenager in England,” Jordan recalls.

His fondness for historical precedent, he says, is critical to his success as a pharmacologist. For the better part of a century, he says, nobody could understand why estrogen killed breast cancer in a certain subset of women. However, Jordan remembered Haddow’s research from the 1940s and his graduate student’s serendipitous finding with tamoxifen-resistant tumors from the 1990s. “I believe that we’re all part of this continuum. We’re in a relay race and we’ve got to know where we’ve come from to show us where we’re going,” he says.

That focus has earned Jordan innumerable awards, but the honor for which Jordan remains most proud is one bestowed upon him by Northwestern University and the family of the late Diana, Princess of Wales. A longtime supporter of women’s health initiatives, Princess Diana came to Chicago to support a symposium hosted by People magazine on women’s health and breast cancer. Jordan organized the event, and the two became friends. When Princess Diana died in a car accident in 1997, her family suggested establishing a professorship in her honor, earning Jordan the title Diana Princess of Wales Professor of Cancer Research at Northwestern University.

Chance encounters and obsession, Jordan says only half in jest, are key to his success. “Early on, I developed key concepts, and like a dog with a bone I never let those concepts go.”

Sujata Gupta, Freelance Science Writer