Designer Estrogens

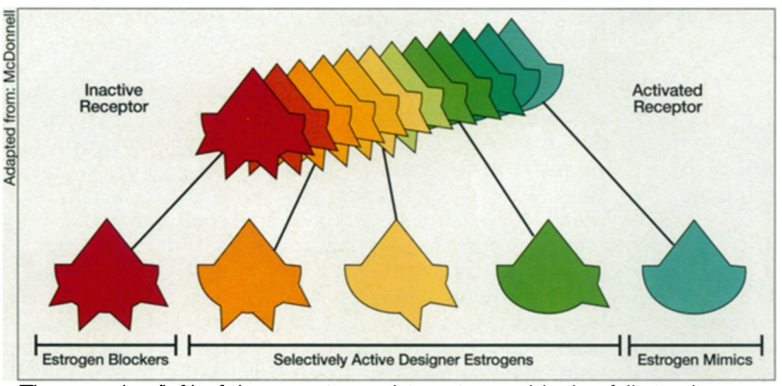
Getting all the benefits, few of the risks

By DAMARIS CHRISTENSEN

It's the dream of every doctor and patient: a potent treatment with no unwanted side effects. Such selectivity is easier to imagine than to develop, especially for compounds that have multiple effects in the body.

It's not an impossible dream, however. Scientists in 1992 made a surprising finding about a substance developed to treat breast cancer by blocking the effects of the female sex hormone estrogen. The drug turned out to counter estrogen's action in some tissues, but it acted like estrogen in others. This synthetic hormone may lead the way to other compounds, in the group known as designer estrogens, that will be even more selective.

"The ultimate goal is to have all the beneficial effects of estrogen but not the adverse effects," says JoAnn E. Manson of Harvard Medical School in Boston.



The complex (left) of the receptor and an estrogen blocker fails to alter gene expression in any cell; the receptor complex (right) including an estrogen mimic causes all the changes associated with estrogen. Designer estrogens push the receptor into intermediate forms (center shapes), which are active in some cells but not in others.

Such a drug might be able to induce the advantages of estrogen treatment in women after menopause: boosts in bone density, improvements in heart function, and perhaps delays in the onset of Alzheimer's disease. It would, at the same time, block estrogen's undesirable effects. Taking hormone-replacement therapy for more than 5 years raises a woman's risk of developing breast cancer, endometrial cancer, potentially life-threatening blood clots, and cataracts.

No novel drug is yet able to improve upon postmenopausal estrogen-replacement therapy. Two designer estrogens are currently on the market, however, one to treat breast cancer and one to prevent bone loss that can lead to the brittle-bone disease osteoporosis. The first works by blocking estrogen's effect in the breast; the second, by mimicking it in bone. Several other designer estrogens are being developed in the lab, and a few are in early human trials.

"This is an enormously exciting class of compounds," says Felicia Cosman of the Helen Hayes Hospital in West Haverstraw, N.Y.

"Although not everyone buys into the concept of using pharmacologic agents to prevent disease, for those who do, these drugs will be used to help prevent diseases related to aging and estrogen deficiency," she predicts.

The excitement over designer estrogens began with what is known as the tamoxifen paradox. Scientists at Zeneca Pharmaceuticals of Wilmington, Del., had synthesized tamoxifen, a variation on the estrogen molecule, in hopes of creating a compound that would prevent natural estrogen from stimulating breast cancer.

The drug was effective and, since its introduction almost 20 years ago, has become one of the most widely prescribed breast-cancer treatments. But physicians were concerned that tamoxifen would also prevent natural estrogen from blocking bone loss—meaning that women who survived breast cancer would be especially susceptible to osteoporosis.

This, however, was not the case. A nationwide, 2-year study reported in the March 26, 1992 NEW ENGLAND JOURNAL OF MEDICINE showed that women on tamoxifen had higher bone-mineral density than women not taking the anticancer drug. The unexpected finding sent researchers scurrying to the lab and the clinic.

Part of the research effort focused on the basic science of estrogen and the molecules known as estrogen receptors. When estrogen molecules bind to their receptors inside a cell, some genes turn on and others turn off.

Scientists have developed variations on the estrogen molecule that still bind to the estrogen receptor. If the cell could not distinguish the variant from natural estrogen, the compound would mimic the hormone in all its effects. Other variants would be so different from estrogen that they would not trigger further effects, and by occupying the receptor, they would prevent estrogen from playing its normal role. Researchers had not expected any variations on estrogen to block some of estrogen's effects but not all of them.

While some scientists were examining the molecular actions of designer estrogens, others were exploring the effects of these drugs on patients. According to a study of 6,600 women sponsored by the National Cancer Institute, tamoxifen can not only treat breast cancer but also prevent its development among high-risk, yet healthy women (SN: 4/11/98, p. 228).

Unfortunately, tamoxifen, like estrogen, also raises the risk of endometrial cancer, blood clots, and cataracts. Because of these serious, well-established side effects, tamoxifen is unlikely to be prescribed for routine postmenopausal treatment.

Once tamoxifen's promising effect on bone loss had been demonstrated, scientists at Eli Lilly and Co. in Indianapolis took a new look at an estrogen variant that had proved a disappointing alternative to tamoxifen for treating breast cancer in earlier tests. They discovered that this drug, like tamoxifen, prevents bone loss. In 1997, the Food and Drug Administration approved the drug, now called raloxifene, to prevent osteoporosis.

Raloxifene shares some but not all of tamoxifen's drawbacks. It increases the risk of blood clots but not of endometrial cancer. It may also share some of tamoxifen's benefits.

A 3-year follow-up to the major study proving that raloxifene blocks bone loss provided encouraging evidence that, like tamoxifen, it can prevent breast cancer. Among more than 7,700 postmenopausal women with low bone density, those taking raloxifene were only one-fourth as likely to develop breast cancer within 3 years as those taking a placebo (SN: 6/19/99, p. 388).

The benefits and side effects of these

drugs and newer variations on estrogen are still being described. Two large studies that may answer important questions within 5 years are now under way. In one, which will include about 22,000 women, researchers are testing raloxifene and tamoxifen head-to-head to see which one prevents breast cancer more effectively and with fewer side effects. The second study is looking at 10,000 women to determine whether raloxifene benefits the cardiovascular system.

Definitions of the perfect designer estrogen may vary depending on the patient. None of the estrogen variants now available treats hot flashes and other symptoms of menopause, Manson says. Raloxifene, in fact, worsens hot flashes.

Furthermore, basic research doesn't always predict clinical effects. "Some of these designer estrogens will have effects on tissues that were not anticipated," predicts Manson. Large-scale clinical trials of a designer estrogen known as idoxifene were recently canceled after several years because, like estrogen and tamoxifen, the compound seemed to boost a woman's chance of developing endometrial cancer.

Nonetheless, doctors who treat breast cancer and osteoporosis are excited by current progress, says Adele L. Franks of the Prudential Center for Health Care Research in Atlanta. Raloxifene's apparent ability to prevent breast cancer provides "solid encouragement" that the first designer estrogens will live up to their promise, Franks says.

Tamoxifen and raloxifene were both originally developed to treat cancer, not to selectively block or mimic estrogen's effects. A growing knowledge of how designer estrogens work "intensifies the anticipation of finding something even better than raloxifene," Franks says. "We bumble upon something interesting—like the tamoxifen paradox—and very profound things happen in the process of trying to figure it out."

When the tamoxifen paradox first came to light, researchers knew of only one cellular receptor for estrogen. For tamoxifen or other designer estrogens to have differing effects in various organs, several kinds of estrogen receptors might be involved, scientists speculated. Each type of tissue might have a different combination of receptors.

Evidence for this scenario appeared in 1996, when researchers discovered a second estrogen receptor in rat prostate glands and ovaries. Others soon found that the original estrogen receptor, now dubbed ER-alpha, and the new find, ER-beta, are unevenly distributed in the body. Cells of the pituitary gland, uterus, testis, kidney, and adrenal glands harbor only ER-alpha receptors. Cells in the ovary, testis, prostate, and thymus have only ER-beta receptors. Both estrogen receptors are present in bone, breast, and brain.

"The biological impact of ER-beta remains under analysis," says Benita S. Katzenellenbogen of the University of Illinois at Urbana-Champaign. She suspects that the discovery of the second receptor may explain some of the tissue selectivity of the designer estrogens. Her group has developed new variants of estrogen that selectively bind to one or the other of these receptors, she reported in the February ENDOCRINOLOGY.

Other scientists are less willing to give ER-beta a role in the actions of designer estrogens, which are also called selective estrogen receptor modulators, or SERMS. So far, there is no evidence that tamoxifen, raloxifene, and idoxifene consistently distinguish between the two receptors, says Donald P. McDonnell of Duke University Medical Center in Durham, N.C.

Even two receptors are not enough to explain the tissue-selective effects of tamoxifen, raloxifene, and other designer estrogens under development, he says. He suggests that the crucial difference resides in the shape that the estrogen receptor assumes once estrogen or a variant has bound to it, a combination known as an estrogen-receptor complex. In the March 30 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, McDonnell and his group reported that each of the 10 designer estrogens that they tested forced the activated estrogen receptor into a different shape.

"In addition to the 'on' and 'off' conformations proposed in classical models of estrogen receptor action, it is now apparent that intermediate conformations are possible, each of which seems to be associated with a different spectrum . . . of activities," says McDonnell.

In the July 30 SCIENCE, his team reported that a small compound that blocks estrogen's activity doesn't block tamoxifen's estrogenlike activity. This is further confirmation that the shape of the estrogen receptor changes when it is bound to different compounds, and for the first time confirms that the shape of the estrogen receptor affects its activity, he says. "We've been able to really prove the link between shape and biologic activity," says McDonnell.

Bert W. O'Malley of the Baylor College of Medicine in Houston adds to McDonnell's model. Some cells, he proposes, are more likely than others to respond to particular shapes of the activated estrogen receptor and turn genes on or off.

O'Malley also suspects that in cells, proteins called regulatory molecules enhance or suppress the effectiveness of receptors bound to various estrogens. Studies have identified about 30 different estrogen-receptor–enhancing, or coactivator, proteins, and a few receptor-suppressing, or corepressor, proteins. In 1997, O'Malley and his colleagues at Baylor showed that the relative levels of coactivators and corepressors could reduce or strengthen the effects of tamoxifen in different cells.

Researchers are finding these regulatory proteins in different amounts in various tissues. This uneven distribution could explain the tissue-specific effects of

Closing the gender gap

Men needn't feel left out as pharmaceutical companies pursue novel designer estrogens. Many companies hope to develop a designer estrogen, or selective estrogen receptor modulator (SERM), that men can take to prevent heart disease. First, though, scientists need to develop an estrogen that does not promote breast growth—a side effect few men are willing to tolerate.

"Men have a higher risk of heart disease, and this is presumably related to a lack of estrogen," says JoAnn E. Manson of Harvard Medical School in Boston. "SERMs might have a role in narrowing the heart-disease gap between men and women."

The basic molecular biology of the estrogen receptors seems to hold true for other hormone receptors, says Donald P. McDonnell of Duke University Medical Center in Durham, N.C. This means that researchers can create designer drugs with selective effects on these receptors, he says.

Some scientists are considering androgen, the male sex hormone. Selective androgens that build muscle and bone—but avoid the unwanted hair growth triggered by natural androgen—could help treat the muscle wasting caused by cancer or AIDS, says McDonnell. A few studies have suggested that small amounts of androgen may increase a woman's libido. Because androgens can trigger prostate cancer, it's important to ensure that any designer androgen prescribed to men has little effect in the prostate, says Andrés Negro-Vilar of Ligand Pharmaceuticals in San Diego.

Researchers are also looking to design variations on glucocorticoids, which physicians often prescribe to reduce inflammation in chronic diseases like arthritis in both sexes. Natural glucocorticoids increase a patient's risk of developing hypertension, diabetes, and osteoporosis.

Finally, progesterone, a female sex hormone frequently prescribed to women as a contraceptive, has several unwanted side effects. It can trigger mood swings, fluid retention, and breast tenderness. Drug companies hope to develop selective progesterone-receptor modulators with none of these side effects.

Designer androgens, glucocorticoids, and progesterones have just begun to be tested in people, but Negro-Vilar is optimistic. After all, he says, "once we learned it could work for the estrogen receptor, why not for others?" —*D.C.*

designer estrogens, O'Malley says.

"Different shapes [of the receptor-estrogen complex] attract different regulatory molecules" that themselves activate different genes, he says. "This may also help explain why the same hormone affects different people differently. People have slightly different proportions of coactivators and corepressors."

One question that has perplexed researchers is, Why are estrogen receptors so flexible about the compounds they bind? The observation that estrogen does not exist in just one natural form, but several, may provide an answer. Scientists have long known about the natural variants but believed that they all have the same effect. New research suggests that each of these naturally occurring estrogens has a subtly different effect.

In a study of 30 postmenopausal women, one natural variant of estrogen, called dehydroestrone sulfate, was effective in preventing hot flashes. It did not, however, seem to lower the amounts of fatty acids in the women's blood, suggesting that this estrogen doesn't benefit the heart.

These findings indicate that naturally occurring estrogens work selectively, says Andrés Negro-Vilar of Ligand Pharmaceuticals in San Diego. He and his colleagues reported their results in the June JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM.

"These data suggest that there are naturally occurring estrogens which can act as bona fide SERMs," says McDonnell. However, it will take a great deal of research to tease out their different activities, he says.

The more that basic research illuminates the natural function of the estrogen receptor, the better insight drug developers will have for creating new designer estrogens, he says.

Despite the progress scientists have made in understanding actions of designer estrogens, their long-term use is fraught with complications. "We're very excited about the potential of SERMs, but there is still a lot of work to do, especially on the long-term safety," cautions Franks. "To give a drug to a basically healthy person with the intention of preventing disease, you need to be very sure the benefits outweigh the risks."

Even the well-accepted benefits can be hard to weigh precisely. Despite many reports that estrogen therapy reduces heart disease, a U.S. study of almost 3,000 postmenopausal women who had already had a heart attack found that those given hormone-replacement therapy were just as likely to die of heart disease as were women given a placebo, Stephen B. Hulley of the University of California, San Francisco and his colleagues reported in 1998.

"Overall, we don't know for sure whether raloxifene—or even estrogen—reduces heart disease, " says Manson, although she suspects that both do. "It's going to be decades until we have a clear picture of all the benefits and risks of different SERMs."

One could make the case that until long-term trials are completed, physicians shouldn't prescribe any designer estrogen for extended use, she says. However, Manson also points out that few of the current drugs for preventing heart disease and osteoporosis have undergone long-term trials.

As the baby boomers reach retirement age, the need to judge the costs and benefits of hormone-replacement therapy presses on more women than ever before. If the promise of designer estrogens comes true, a woman's decision about whether to take a drug to combat postmenopausal health problems could become much simpler. Researchers agree, however, that there is no perfect designer estrogen—yet. □

Archaeology

Tool time in the Stone Age

Neandertals pursued a variety of toolmaking strategies in their settlements, showing an aptitude often attributed only to modern humans, according to an investigation of Stone Age artifacts in a Spanish rock shelter.

This finding adds to evidence that behaviors long assumed to have originated among modern humans beginning around 40,000 years ago actually appeared much earlier among other *Homo* species, including Neandertals (SN: 7/3/99, p. 4).

Manuel Vaquero of Universitat Rovira i Virgili in Tarragona, Spain, analyzed the spatial distribution of numerous stone implements from two sediment layers in northeastern Spain's Abric Romaní rock shelter. All the tools display a manufacturing style previously linked to Neandertals.

The upper soil layer, already dated at around 45,000 years old, shows signs of brief occupations by small groups, Vaquero contends. Stone tools and debris from toolmaking form three small clusters. Artifacts consist of relatively small, easily fashioned cutting instruments, each of which was prepared from start to finish at workstations set apart from other activities.

The lower layer, dated at about 50,000 years old, presents a contrasting picture of extended occupations by large groups, Vaquero reports in the September ANTIQUITY. Many stone-tool clusters surround a central accumulation, arranged so that large, sharpened flakes could be fashioned in stages at a succession of workstations. Toolmaking proceeded in areas also used for cooking and other domestic chores, another sign of long-term residence, Vaquero says.

In a related analysis of Stone Age tool traditions, Ofer Bar-Yosef of Harvard University and Steven L. Kuhn of the University of Arizona in Tucson conclude that elongated stone blades with sharpened points, often treated as an invention of modern humans around 40,000 years ago, appeared as early as 300,000 years ago among various members of the *Homo* lineage (SN: 4/11/98, p. 238).

Blades only came to dominate the archaeological record of western Europe and Asia, as well as parts of Africa, after 40,000 years ago, the researchers note. This may reflect manufacture of increased numbers of replaceable blades for tools with handles, Bar-Yosef and Kuhn proposed in the June AMERICAN ANTHROPOLOGIST. —*B.B.*

Well-aged slabs of art

Radiocarbon analysis of minute pigment samples taken from two painted rock slabs places their age at a minimum of 3,600 years, providing the oldest direct evidence for cave or rock art in southern Africa. European cave art dates back 30,000 years.

Scientists have surmised, based on the ages of associated finds, that people painted the walls of caves and rock shelters in this region as long as 27,000 years ago (SN: 10/5/96, p. 216). Until now, however, radiocarbon dates for rock-art pigments in southern Africa extended back 500 years at most.

Ongoing radiocarbon studies should continue to push back confirmed dates for southern African rock-art, say Antonieta Jerardino of the University of Cape Town, South Africa, and Natalie Swanepoel of Syracuse (N.Y.) University.

The scientists studied painted slabs unearthed in a burned deposit at Steenbokfontein Cave, located near South Africa's west coast. What remains of one scene shows three pairs of human legs and hips painted in red, with a white robe on one figure. The other depicts four red pairs of human legs and hips, with rows of white lines and dots on one set of knees and ankles.

A fire in the cave caused its walls to crack and dislodged the slabs, resulting in their burial, say Jerardino and Swanepoel in the August–October CURRENT ANTHROPOLOGY. The fire destroyed parts of the painted slabs and obliterated any images that had been painted on eight other slabs in the same deposit. —*B.B.*