

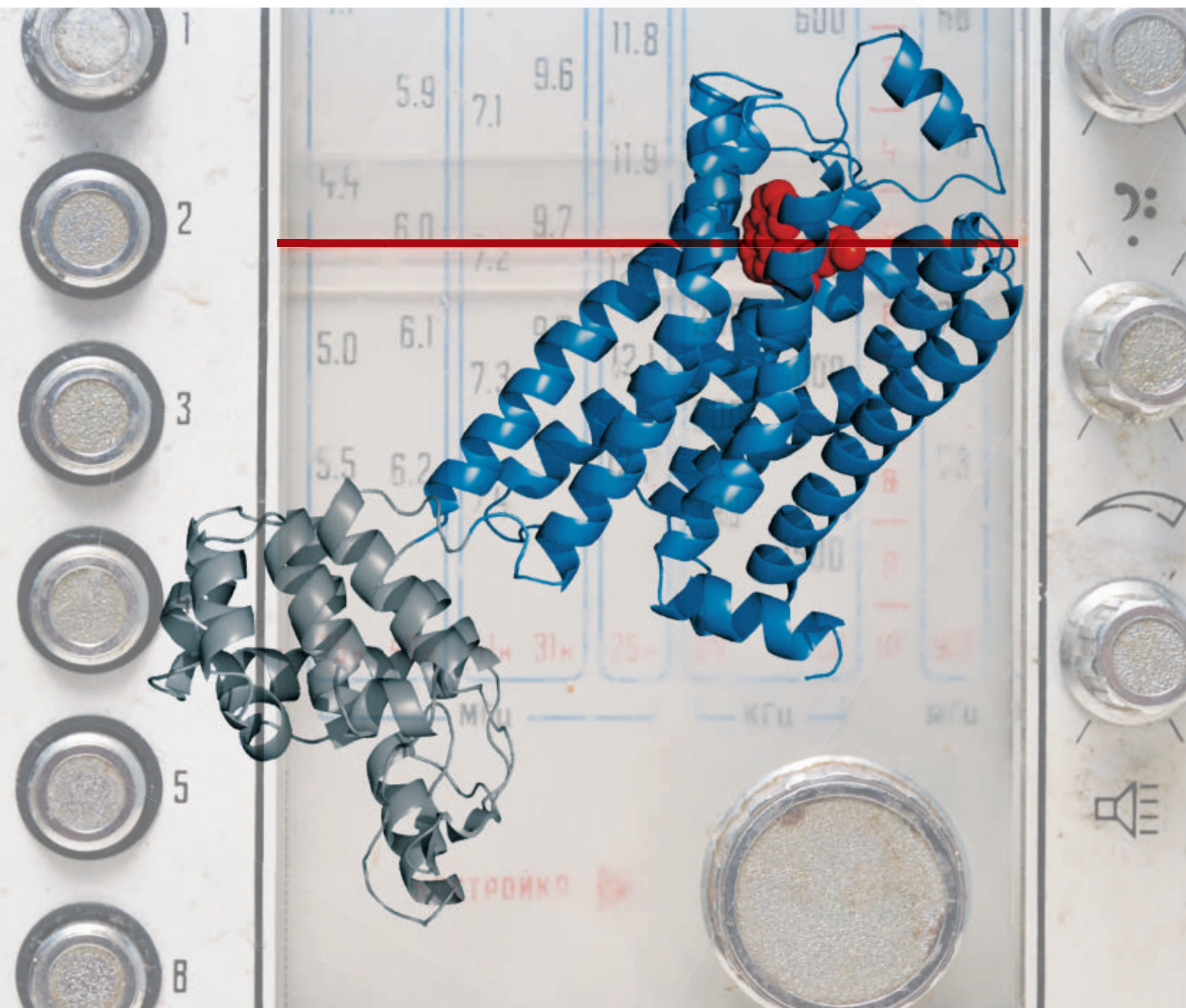
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# C&EN

CHEMICAL & ENGINEERING NEWS

**BIOTECHNOLOGY**  
Spanish industry tries  
to catch up **P.19**

**GEOENGINEERING**  
Schemes to cool Earth  
gain traction **P.28**



## TUNING THE SIGNAL

Making drugs that adjust receptor activity **P.12**



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# HOT FLASHES: STILL A MYSTERY

Researchers develop new treatments without fully understanding this common **SYMPTOM OF MENOPAUSE**

SOPHIE L. ROVNER, C&EN WASHINGTON

**THE TRANSITION** to menopause goes smoothly for some women, but for others it can be hellacious. While coping with the mixed blessings of the end of menstruation and loss of fertility, women may experience a host of symptoms that some jokingly say makes them want to commit murder.

The transition—known as perimenopause—usually begins in a woman’s 40s, according to the North American Menopause Society. Perimenopause can last six years or more and ends, on average, by age 51. Hot flashes (also called hot flushes) are the most common menopause-related symptom and affect 75% of women in Western societies, notes Robert R. Freedman, a professor in the psychiatry and behavioral neurosciences department at Wayne State University School of Medicine who has studied hot flashes extensively.

Hot flash episodes generally last just a few minutes each and typically recur over a span of two to four years. But some 15% of women have to endure them for two decades or more, says Charles L. Loprinzi, an oncologist at the Mayo Clinic, in Rochester, Minn., who has spent about 20 years studying the efficacy of hot flash treatments.

Hot flashes can be fairly mild, as they were for Bonnie, who is now 56. “It’s like standing a little too close to a roaring fire,” she tells C&EN. “Your face gets really hot and a little flushed. You feel like you have a sunburn.” Turning on a fan or applying a damp towel was a sufficient remedy, she says.

Bonnie’s experience with hot flashes was fairly innocuous,

but others aren’t so lucky, notes Ruth G. Freeman, an endocrinologist, internist, and professor of medicine and obstetrics at Yeshiva University’s Albert Einstein College of Medicine, in Bronx, N.Y. One of Freeman’s patients would pour sweat all over the papers on her desk when she was in the grip of a hot flash—and they would flare up five to 10 times a day.

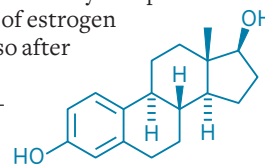
Fortunately, many women can get their hot flashes under control with the help of medication. Current treatments

aren’t suitable or effective for all women, however, and research to develop alternatives continues. Meanwhile, scientists and physicians are trying to add to the meager data about the physiology and biochemistry of hot flashes.

**WHAT IS KNOWN** is that hot flashes and the other symptoms of perimenopause follow a decline in function of the ovaries, which causes their production of estrogen and progesterone to fluctuate—sometimes wildly—and eventually cease. Other tissues in the body that produce a small amount of estrogen continue to do so after menopause.

The term “estrogen” actually refers

to a group of hormones, including 17 $\beta$ -estradiol and its metabolites, estrone and estrinol, that play a key role in



**17 $\beta$ -Estradiol**

the development of female characteristics and in the reproductive process. Estrogen circulates in the bloodstream and binds to receptors on cells in the breasts, uterus, ovaries, brain, bone, lung, liver, heart, and other tissues, thereby helping to regulate gene expression, among other functions. Two types of estrogen receptors have been identified, known as ER $\alpha$  and ER $\beta$ . Their relative distribution varies from tissue to tissue.

The connection between hot flashes and estrogen loss is believed to depend on estrogen’s activity in the brain, says Freeman, who has carried out considerable research on reproductive hormones and estrogen replacement. Estrogen decline subtly alters the function of the hypothalamus, which controls body temperature, she explains. The result is that it “says the body should be cooler,” she says. “And to cool off, you increase blood flow in the skin, you start to perspire, and you speed up your heart rate. That’s what the hot flash is; it’s an attempt to cool the body. If you measure the temperature inside the body after a hot flash, it goes down 1 °C.”



ISTOCK

Wayne State's Freedman has studied women's core body temperature and found that both the mean temperature and fluctuations in temperature are essentially the same whether a woman is prone to hot flashes or not.

Freedman has also measured the range between the room temperature at which a woman starts to sweat and the temperature at which she starts to shiver. He found that this temperature gap is considerably smaller in women who suffer from hot flashes.

Still, it's not clear what makes a particular woman susceptible to hot flashes or what kicks off a hot flash. Estrogen levels are equivalent in menopausal women who suffer from hot flashes and those who don't. However, both the initial level of estrogen prior to perimenopause and the rate of decline during the transition appear to affect the intensity of symptoms.

For example, women whose estrogen production is naturally low before menopause—and who therefore don't develop typical female body characteristics—“never get into trouble with hot flashes,” Loprinzi says. But if one of these women undergoes estrogen therapy and then stops taking the hormone, she will get hot flashes.

Hot flashes are a particular problem for women who suffer an abrupt loss of estrogen as a result of ovary removal or chemotherapy that suppresses the body's production of estrogen to reduce breast cancer risk, Loprinzi says.

Not surprisingly, the most effective treatment for hot flashes is estrogen, which Freedman has shown raises the temperature at which a woman begins to sweat.

ONE OF THE MOST common estrogen therapies is based on conjugated estrogens. These compounds can be produced synthetically or derived from natural sources such as the urine of pregnant mares. One such treatment is Premarin, which contains sodium estrone sulfate, sodium equilin sulfate, and other ingredients. Alternatives such as Menest and Estratab contain esterified estrogens

derived from mare urine or plant sources. Estradiol is available in products such as Estrace and Alora.

To avoid side effects, estrogen therapy is typically provided at the lowest dose for the shortest time possible, often for fewer than five years. When women are ready to stop taking estrogen therapy, they need to taper off the dose over a year or so to prevent the return of hot flashes, Yeshiva University's Freeman notes.

The hormone progesterone works nearly as well as estrogen, according to Loprinzi. The progesterone derivatives megestrol acetate (Megace) and medroxyprogesterone acetate (Provera) are also effective, he notes. Progesterones have also been combined with estrogen in products such as Prempro and Ortho-Prefest.

Some women are reluctant to take traditional hormone therapy because it can drive up the risk of heart disease, stroke, and breast cancer. These side effects are believed to derive, at least in part, from the fact that current estrogen therapies activate both the  $\alpha$  and  $\beta$  estrogen receptors.

Researchers are therefore pursuing selective estrogen receptor modulators that discriminate between ER $\alpha$  and ER $\beta$ . For example, Bionovo, an Emeryville, Calif., pharmaceutical company, is preparing a Phase III clinical trial of the experimental treatment Menerba, which selectively activates ER $\beta$ .

Formerly known as MF101, the drug is an extract derived from a combination of 22 herbs traditionally used in China to treat menopausal symptoms. One of Menerba's active ingredients was recently identified as the flavanone liquiritigenin, a component of licorice (Mol. Cell Endocrinol.2008, 283,49).

Meanwhile, Radius Health, a drug company in Cambridge, Mass., is testing a selective estrogen receptor modulator dubbed RAD1901 in a Phase IIa clinical trial. The compound was discovered by Tokyo-based pharmaceutical company

Eisai, which licensed most of the rights to RAD1901 and its analogs to the U.S. firm. Radius notes that the compound's ability to penetrate the blood-brain barrier allows it to relieve hot flashes by activating estrogen receptors within the central nervous system.

Several other nonhormonal treatment options are available to hot flash sufferers. They include the antiseizure medication gabapentin (Neurontin) and the pain and epilepsy medication pregabalin (Lyrica).

Antidepressants that increase the amount of the neurotransmitter serotonin in the brain are also effective, Loprinzi says. For instance, paroxetine (Paxil) and venlafaxine (Effexor) work well. His own recent study indicates citalopram (Celexa) also works, whereas fluoxetine (Prozac) and sertraline (Zoloft) appear to work to a lesser extent, he says.

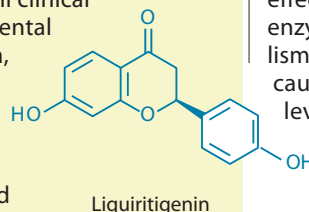
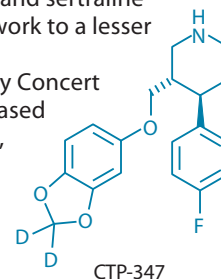
Biotech company Concert Pharmaceuticals, based in Lexington, Mass., has developed the paroxetine analog CTP-347 as a potential hot flash treatment that boosts serotonin levels.

Paroxetine itself has an unpleasant side effect: It irreversibly inactivates a liver enzyme that is necessary for the metabolism of many other common medications, causing them to build up to dangerous levels in patients. Concert created CTP-347 by replacing a couple of paroxetine's hydrogens with deuterium.

The substitution significantly reduces the drug's tendency to inactivate the liver enzyme (C&EN, June 22, page 36). Concert hopes to find a partner to further develop the drug.

There seems to be a yin and yang relationship between serotonin and the neurotransmitter norepinephrine, in which an increase in the amount of serotonin decreases the level of norepinephrine, Loprinzi says.

Norepinephrine's role in hot flashes is supported by a number of findings. For instance, some data suggest that the



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decline in estrogen that occurs in menopause raises levels of norepinephrine in the brain, Loprinzi says. Norepinephrine is involved in the body's temperature regulation, according to Freedman. And the blood-pressure-lowering medicine clonidine (Catapres), which has also found success in treating hot flashes, reduces norepinephrine levels in the brain, he notes.

Eugene G. Lipov, medical director at Advanced Pain Centers, in Hoffman Estates, Ill., has shown that a pain-relief procedure known as stellate ganglion block offers relief from hot flashes. In this procedure, a physician injects anesthetic into the neck near the stellate ganglion, a mass of nerve cells that help regulate blood flow and sweating. These cells are connected to the insular cortex, a brain region activated during hot flashes. Lipov believes that the technique resets the signals sent from the stellate ganglion to the brain through a prolonged reduction in nerve growth factor, which in turn decreases the amount of norepinephrine in the brain (*Med. Hypotheses* 2009, 72, 657).

**SOME WOMEN** find relief with the help of supplements, herbal remedies, and specific foods. Researchers attribute at least some of this success to the placebo effect. Roughly 20% of women see a 75% reduction in hot flashes with just a placebo, Loprinzi says.

Vitamin E, for instance, works only about as well as placebo, Loprinzi says.

Results are mixed for foods that contain phytoestrogens, which are a class of isoflavones that can bind to estrogen receptors. The herb black cohosh doesn't affect hot flashes, for example, and most studies show that soy doesn't help either, according to Loprinzi. On the other hand, some evidence suggests that flaxseed might actually offer some relief. Loprinzi is about to start a clinical trial that will compare flaxseed with a placebo.

Behavioral changes also show some promise. Deep, slow, abdominal breathing can help. Avoiding warm clothing, hot rooms, hot or spicy foods, caffeine, alcohol, smoking, and stress is also beneficial.

Women might want to experiment with different treatments to find the one that suits them best. The particular treatment they choose will depend in part on the menopausal symptoms they suffer in addition to hot flashes. Bonnie had to cope

with night sweats and insomnia, and "the lack of libido was absolutely dreadful," she recalls. "Adding in the thinning hair; the dry, itchy skin; the lack of attention span; and the fact that I wanted to bite somebody—those were the things that sent me to seek treatment."

She first tried the progesterone derivative Provera but didn't care for the side

effects. She then switched to bioidentical hormones. Unlike traditional hormone treatments, which rely on hormones that closely resemble but don't exactly replicate natural hormones, the bioidentical hormones have the same molecular structure as those found naturally in the body. And now, Bonnie says, "I feel the best I've felt since I was 30." ■

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