

Its the hot sleeping pill, natural and cheap. Now scientists say this hormone could reset the body's aging clock, turning back the ravages of time.

Melatonin

BY GEOFFREY COWLEY

TURNING BACK THE CLOCK has long been the domain of crackpots and charlatans. Take one look at the claims that enthusiasts are making for melatonin, a hormone sold as a supplement in health-food stores, and you'll quickly sense that nothing much has changed. "Senescence, the downward spiral that we have come to associate with aging, **does not** have to occur," Drs. Walter Pierpaoli and William Regelson declare in their forthcoming book, "The Melatonin Miracle." "Melatonin can stop the spiral."

Strip away the bombast, and it turns out these guys are on to something interesting. Like most animals, we produce melatonin abundantly throughout early life. But the levels in our blood drop slightly before puberty and decline steadily into old age. When **Pierpaoli**, an Italian immunologist, restores youthful levels of the hormone in mice, they outlive their life expectancies by nearly a third. And his **findings** are consistent with a burgeoning scientific literature. Recent studies suggest that supplementing the hormone may bolster our immune systems, keep our cells from disintegrating, slow the growth of tumors and cataracts, and ward off heart disease. All that while helping us sleep better.

Proven or not, melatonin is

poised to become one of the hottest pills of the decade. It's cheap and readily available — a month's supply costs less than \$10 in **health-food stores** — and it's gaining popularity among people who've heard nothing about its anti-aging properties. Travelers and **office** workers are using it as an antidote to jet lag, stress and insomnia. And sales are soaring. One manufacturer, Source Naturals of **Scotts Valley, Calif.**, expects to move a million jars of lozenges this year — three times the number it sold in 1993. Skeptics cringe at the thought of people gulping down a supplement whose long-term effects are largely unknown. But since studies have yet to document any hazards, even scientists are taking the plunge. "I take a milligram or less every night," says **Russel** Reiter, a University of Texas

cellular biologist who has studied melatonin for 30 years. "I want to die young as late in life as possible, and I think this hormone could help."

First identified just four **decades** ago, melatonin is now recognized as one of life's most ubiquitous molecules. It turns up in such diverse organisms as people and protozoa, suggesting it dates back a billion years or so. Humans secrete it cyclically from the pineal gland, a pea-size structure nestled at the center of the brain, in response to the amount of light hitting our eyes (chart). Physiologists know melatonin as the hormone that keeps us in sync with the rhythms of the day and the season. Through its actions on other hormones, it helps determine when people sleep and

homes breed, when birds migrate, dogs shed their coats and **certain frogs** change color. But cellular biologists have recently discovered that melatonin has an even more basic function, which is to protect oxygen-based life from the toxic effects of . . . oxygen.

Yes, oxygen. As we metabolize this **life-sustaining** gas, we generate highly reactive molecules called free radicals, which can corrode our cellular membranes and damage our DNA. The process, known as oxidation, weakens our minds and muscles as we age, and contributes to at least 60 degenerative diseases, including cancer, heart disease and **Alzheimer's**! The body produces several enzymes to inhibit oxidation, and nutrients such as vitamin C, vitamin E and beta carotene can provide extra protection. But most of these **so-called** antioxidants work only in certain parts of certain cells. Melatonin readily permeates any cell in any part of the body — including the brain. And as Reiter's research team has recently shown in animal experiments, the hormone can protect tissues from an amazing array of assaults.

The evidence started stacking up just two years ago, when Reiter and his colleagues showed that a small dose of melatonin could shield **rats from** a cancer-causing chemical called safrole. Given alone, safrole quickly oxidizes liver cells, causing extensive DNA damage. But when rats got tiny doses of melatonin before their **safrole** shots, they exhibited 41 percent less damage than their untreated counterparts — and those receiving a slightly larger dose of melatonin **suffered** just 1 percent as much liver damage as the controls. In more recent studies, Reiter's team has shown that melatonin's antioxidant action can protect rats from ionizing radiation (halving the death rate from a normally lethal dose), and can shield the animals' lungs from the

Cure-All?

Melatonin's benefits are still debatable, but studies point to many possible uses. The drug may help:

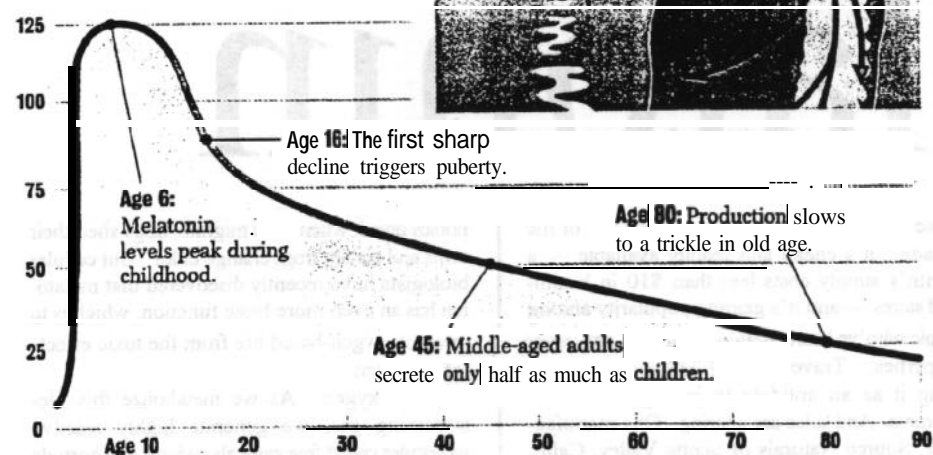
- Ease insomnia
- Combat jet lag
- Prevent pregnancy (in large doses)
- Protect cells from free-radical damage
- Boost the immune system
- Prevent cancer
- Extend life

DAVID **BERKOWITZ**—NEWSWEEK

Regulating the Body's Rhythms

Secreted cyclically from the pineal gland, a pea-size structure nestled at the center of the brain, melatonin keeps us in sync with the rhythms of the day and the season. By orchestrating the action of other hormones, it determines when people sleep and horses breed, when birds migrate, dogs shed their coats and certain frogs change color.

Average nighttime melatonin peaks, in picograms per milliliter of blood



SOURCES: RUSSEL REITER, UNIVERSITY OF TEXAS, HEALTH-SCIENCE CENTER; DIAGRAM: CHRISTOPH BLUMRICH - NEWSWEEK

deadly herbicide paraquat. Melatonin may also help prevent cataracts, the cloudy lesions that appear on our eyes as oxidation damages cells in the lenses. When the Texas researchers gave 18 newborn rats a toxic compound called BSO, all 19 developed cataracts within two weeks. But when 15 animals got the same treatment plus melatonin, 14 maintained perfectly clear eyes.

OXIDATION ISN'T THE ONLY reason we fall apart as we age. We also lose our immune function. The thymus gland shrinks over time, sapping our ability to generate infection-fighting T cells, and we produce fewer of the antibody molecules that bind with and neutralize foreign invaders, such as viruses and bacteria. Could all of this follow from a loss of melatonin? Test-tube studies have identified receptors, or specialized portals, for melatonin on the cells and the glands of the immune system. And animal experiments are showing that the hormone can preserve, or even restore, a creature's defenses.

One of the best examples comes from Pierpaoli's mouse lab. A few years ago he paired 10 young mice with 10 old ones and had a microsurgeon switch their pineal glands (old to young and vice versa). Before long, the youngsters were hobbling around with cataracts in their

eyes and bald patches on their backs. The old ones gained muscle and energy, and their coats grew thick and shiny. Autopsies revealed what was probably part of the reason. The young mice had all but lost their thymus glands after the pineal transplant. The oldsters had theirs restored.

In other animal studies, Italian researchers have shown that a nightly melatonin supplement can boost the performance of immune systems compromised by age, drugs or stress. And scientists in Israel and Switzerland have found that when mice receive melatonin, their odds of surviving infection with an encephalitis virus more than double.

No one knows just how neatly any of these findings will apply to people. But together they suggest that melatonin could help us prevent, and even treat, the most common afflictions of old age. Where cancer is concerned, the evidence isn't limited to mouse studies. Autopsy studies suggest that pineal calcification (a condition that hardens the gland and reduces melatonin output) is most common in countries with high rates of breast cancer and least common in countries where breast cancer is rare. By the same token, women taking chlorpromazine, an antipsychotic medication that raises melatonin levels, enjoy unusually low rates of the disease.

The explanation, says Dr. Michael Cohen of Fairfax, Va., involves estrogen. Prolonged exposure to that hormone (due to early puberty, infrequent childbearing or late menopause) increases a woman's risk of breast cancer. But melatonin dampens the release of estrogen. In fact, high melatonin levels can temporarily shut down the reproductive system. That's why females in most species are fertile only at certain times of year. Exploiting this principle, Cohen has combined a stiff (75 mg) dose of melatonin with progestin to create a new oral contraceptive. The drug, called B-Oval, has performed as well as conventional birth-control pills in European studies involving 1,000 women, and has shown no toxicity, Cohen plans to launch U.S. trials within two years, but his goal is not simply to market another contraceptive. If his hypothesis about melatonin, estrogen and breast tumors bears out, the new pill could help women prevent cancer as well as unwanted pregnancies.

Melatonin may also prove useful for fighting existing malignancies. Several studies have shown that it can slow the growth of human tumor cells in a test tube, and some cancer specialists are now testing its effects on patients. In a 1992 study, Dr. Paolo Lissoni and his colleagues at San Gerardo Hospital in Monza, Italy, found that a nightly melatonin supplement (10 mg) significantly improved one-year survival rates among patients with metastatic lung cancer. The same lab has since reported that melatonin can enhance the effect of interleukin-2 shots (IL-2 is a hormone that helps T cells proliferate) on cancers of the lung, kidney, liver, colon and pancreas. IL-2 causes horrific fevers and nausea at the doses normally required to tame tumors. But Lissoni's group found that the compound is effective at a fraction of the usual dose when accompanied by melatonin.

DEFINING THIS HORMONE'S true powers as an antidote to aging and chronic illness will take years, if not decades. There are countless leads to follow. Animal studies suggest that besides combating cancer, melatonin might help control cholesterol, regulate blood pressure and modulate the release of heart-killing stress hormones. But today's users aren't overly concerned with any of this. Most just want a decent night's sleep — and many will tell you they've found it. Robbie Felix, a 40-year-old employment consultant in Silicon Valley, says she was a "chronic insomniac" until two years ago, when she read about melatonin on the Internet. Since then, she has taken 15 to 20 milligrams every night (three to four times the typical dose), and slept soundly. "With traditional sleeping pills you're groggy the next day," she says. "Not with this." Dr. Steven Bock of Rhinebeck, N.Y., author of a new book titled "Stay Young the Melatonin Way," says he has given the stuff to 300 patients and never seen a bad reaction. Dr. Ray Sahelian of Los

Angeles (author of "Melatonin: Nature's Sleeping Pill") is just as excited. "I think eventually this will make prescription sleeping pills all but obsolete," he says.

There's more at work here than the power of suggestion. Researchers have been documenting melatonin's sleep-inducing properties since the early 1980s, when Dr. Richard Wurtman of MIT's Clinical Research Center started giving volunteers what are now recognized as megadoses (240 mg). Controlled studies have since established that as little as a tenth of a milligram can hasten the onset of sleep, whatever the time of day. Researchers have also shown that a brief nightly regimen of 5 milligrams can help airline workers adjust to new time zones. And Dr. James Jan of Vancouver, British Columbia's Children's Hospital, has reported that bedtime doses of 2.5 to 10 milligrams help establish normal sleep patterns in kids with neurological problems such as autism, epilepsy, Down syndrome and cerebral palsy. "We had tried everything," Jan recalls of the first child he treated with melatonin, "but nothing worked" After one dose of the hormone, "the parents called me and said, 'It's a miracle! A miracle!'"

The child slept through the night."

There are plenty of drugs that can bring on sleep, but they have well-known drawbacks. They tend to suppress the restorative dream state known as REM. The lose their effect over time. They're addictive if used too often, and at high doses they can kill you. Researchers have yet to report any of these problems with melatonin. When government scientists set out to find melatonin's "LD 50"—the dose that's lethal to 50 percent of the animals receiving it—they couldn't make a rich enough concentrate to kill a mouse. And when researchers fed human volunteers 6 grams (6,000 mg) of the stuff every night for a month stomach discomfort and some residual sleepiness were the only reported side effects. Even so, experts differ sharply on whether melatonin should be sold like seaweed in health stores. "Every time someone writes about this stuff," says Wurtman, "I get the sinking feeling that more people are going to run out and take it." Wurtman is as excited as anyone about the hormone's potential. His own company, Interneuron Pharmaceutical, has a patent pending on a melatonin-based sleeping pill (the chemical itself can't be patented). But he

worries that we know less about the hormone than we think we do. "Is it safe to take while you're pregnant?" he asks. "Is it safe to take with Prozac? No one really knows." if the FDA regulated melatonin as a drug, manufacturers would have to address such questions before marketing it. They would also have to show that their ingredients were pure and their production methods sound. Says Wurtman, "You'd have a better idea of what you were buying."

For now, consumers are stuck deciding for themselves whether to trust what they read on a label. There's no reason to assume that melatonin is any more hazardous than other unregulated supplements. And as enthusiasts like to point out, regulated prescription drugs still carry plenty of risks. So far, the FDA has shown little interest in controlling melatonin. The agency simply warns users that they take it "without any assurance that it is safe or that it will have any beneficial effect." It's a worthy admonition, but it's not likely to turn people away. The promise is too rich; a good night's sleep, complete with dreams of a rip-roaring 105th birthday party.

With JAMIE RENZI in San Diego,
MARY HAGER in Washington and
AMY SALZHAUER in New York

Natures Other Time-Stopper?

MELATONIN ISN'T THE only hormone showing promise as an antidote to aging. Some experts are equally excited about a substance called DHEA (dehydroepiandrosterone), which has a number of similar effects. At a recent conference sponsored by the New York Academy of Sciences, researchers from around the world presented preliminary evidence suggesting that DHEA might help strengthen aging bones, muscles and immune systems, while providing a new weapon against lupus, diabetes and cancer.

DHEA is made in the adrenal glands (which sit atop the kidneys) and helps generate the sex hormones estrogen and testosterone. Production rises dramatically during puberty. But like melatonin, DHEA wanes as we age, and our bones, muscles and immune systems seem to wane with it. The benefits of replenishing

DHEA and its less-active relative **DHEAS** are still unclear. But researchers in Salt Lake City recently reported **DHEAS** helped elderly people respond more effectively to a flu vaccine. And Dr. Samuel Yen of the University of California, San Diego, has found that aging vol-

unteers given daily doses enjoy "increased ability to cope with stress, increased quality of sleep, decreased joint pain, increased joint mobility" and improved mood.

Animal studies suggest DHEA can cause liver damage at high doses, but health-food stores sold oral supplements until 1985, when the FDA banned the practice. No one is now licensed to market the hormone. Doctors can still prescribe it, and pharmacies can mix it on their own. But without commercial suppliers, DHEA isn't likely to match melatonin's popularity any time soon.



LESTER SLOAN—NEWSWEEK
Looking for youth in a capsule: DHEA