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Drugs that might extend human life are one of the hottest topics in biotech. Some of them are already here. BY DAVID STIPP

Chasing the Youth Pill

PERSONAL FORTUNE HEALTH

The power of wishful thinking guarantees that just about anything can be successfully marketed as an elixir of youth. Pee, for instance. A multitude of websites extol the ability of "urine therapy"—yes, the idea is to gulp it down—to ward off whatever might ail you, including aging itself. Or you can try bottled water from a town in Ecuador whose inhabitants, according to Internet ads for the stuff, never get cancer, diabetes, heart attacks, or other diseases of aging. Water and snake oil, it seems, actually do mix.

But it would be a mistake to dismiss the entire anti-aging enterprise as a quacks' bazaar. Over the past few years the area has become a hot topic in serious science. A raft of studies on potential anti-aging drugs are getting underway, thanks to a project recently launched by the federal National Institute on Aging. Groups of mice will be fed substances suspected of retarding aging and followed to see whether their average lifespans exceed those of untreated groups. The goal isn't to find youth pills, says Huber Warner, head of the Institute's Biology of Aging Program, but to identify drugs that foster a healthier old age; compounds that lengthen mouse lives may well ward off ills like

Caloric restriction fact

- **Animals fed 30% to 40% fewer calories live 30% to 40% longer.**

cancer, which shorten the lives of rodents as well as people. Modern Ponce de Leóns will be following the project with intense interest.

The project's initial reports are two or three years away. But the message is already plain: Drugs that extend human life and confer a healthier old age are probably coming—perhaps not fast enough to make much difference to the baby-boom generation, but probably soon enough to have a big impact on people now under 30. How many more years of life might such drugs grant us? Let's look at mice. One of gerontology's boldest optimists, Aubrey de Grey at Britain's University of Cambridge, predicts that in a decade or so scientists should be able to actually reverse the effects of aging in mice. Interventions begun at age 2, de Grey believes, will boost the rodents' expected remaining life from one year to three—a mind-boggling 200% increase.

Mouse rejuvenators may not do the same for us. But even a drug that modestly slows human aging—extending the average lifespan by, say, 15%—would change everything. Imagine millions following the long trail blazed by France's Jeanne Calment, who smashed the world longevity record before dying in 1997 at age 122. Famously vibrant, she bicycled until she was 100, and at 121 released a CD of reminiscences set to rap and other music—pretty impressive for someone born before the invention of the phonograph.

Scientists know how to extend animals' lifespans: Put them on low-calorie diets.

One reason for the optimism about extending the human lifespan is that scientists already know how to do it in animals: by putting them on low-calorie diets. The miracle of caloric restriction, or CR, was discovered in the 1930s and has been shown to work in everything from yeast to spiders to rats. The equation is simple: Animals fed 30% to 40% fewer calories than they usually prefer to eat generally live 30% to 40% longer. Ongoing CR studies with monkeys are expected to yield similar results. The calorie-restricted monkeys, now middle-aged, show multiple signs of slowed aging, such as youthfully low blood pressure and even youthful looks.

The fact that CR works wonders in such a broad array of animals suggests that it could delay aging in humans too, says George Roth, a senior guest scientist at the National Institute on Aging and the co-author of many major CR studies. Recently the institute launched the first major CR-related study in humans. Expected to last only two to three years, the study won't be able to say for sure whether CR extends human life. But by tracking participants' risk factors for diseases of aging—cholesterol levels, blood pressure, and the like—researchers will pin down much of what CR actually does for people. Some true believers aren't waiting for the results: They've put themselves on CR diets already (see the sidebar that follows this story).

No matter how well CR works in people, the maniacal stoicism it demands will be too much for most. How many of us are willing to eat like birds for the rest of our lives—and to endure the bony frames, constant chill, and lowered libido that frequently accompany a CR regime? That's where drugs might come in. At least half-a-dozen biotech startups are researching whether drugs can mimic CR's effects while letting you eat dessert. They include Elixir Pharmaceuticals of Cambridge, Mass., LifeGen Technologies of Madison, and BioMarker Pharmaceuticals of Campbell, Calif.

Their work has been aided by the discovery of genetic mutations over the past 15 years that increase lifespan by 50% or more in yeast, worms, fruit flies, and mice. Probing the mutants has yielded many clues about what kind of molecular tweaking might emulate caloric restriction. Most of the life-extending genes identified so far regulate growth and energy metabolism. Four of the half-dozen anti-aging mutations known in mice, for example, block growth hormone. Not surprisingly, the long-lived rodents are unusually small. They're also infertile and have other hormonal glitches, and they get cold easily.

Deep down, though, long-lived mutants are tough as old jerky—the altered genes that prolong their lives appear to boost cellular defenses against all kinds of insults. Cells of so-called p66shc mutant mice, which live 30% longer than normal, can survive doses of radiation or of toxins that kill cells of nonmutated mice.

The mutants' idiosyncrasies sup-

Life expectancy fact

- **Today men in the U.S. can expect to live to age 74.4; women, to 79.8.**

port a theory that explains everything from the marked longevity of dwarf animals like Chihuahuas to the infertility of anorexic women. Its key idea is that aging slows when food is scarce. This "famine response" takes energy normally expended on growth and reproduction and redirects it to harden cells against wear and tear. That enables an animal to last through a food shortage so that it can reproduce later.

Caloric restriction is thought to switch on the response. Mutations that slow aging may turn on the response too, or perhaps key aspects of it. Since their effects are exerted during early development, they often have a far more lasting and profound impact than does caloric restriction in later life. Even genes that mildly slow early growth, reducing adult stature, may extend lifespan. A study of deceased professional baseball players, for example, found that for every extra inch of height, a player died, on average, 1.2 years earlier than his shorter teammates.

Psst: Want another six years?

Here's how much time eight behaviors may add to the life of the average guy in his 40s. Doing them all buys him six more years.

BEHAVIOR	TIME GAINED
Get stress under optimal control	1.5 YRS.
Drop blood pressure to 115 over 76	1.3 YRS.
Walk/exercise 90 minutes a day, seven days a week	1 YR.
Give up a pack-a-day smoking habit for five years	11 MOS.
Take the right vitamins; avoid the wrong ones	10 MOS.
Floss and brush daily	5 MOS.
Have good sex 14 times a month	3 MOS.
Have one or two drinks a day	2 MOS.

FORTUNE TABLE / SOURCE: REALAGE

Researchers are racing to fill in details of this big picture—and to turn their findings into drugs. The goal will be to tease apart the effects of famine response and activate only desirable aspects of it with medicines. The fact that long-lived small dogs are fertile and vigorous makes a compelling case that this goal is at least partly achievable. Some of this pursuit's most intriguing advances over the past few years have sprung from the lab of Leonard Guarente, a Massachusetts Institute of Technology biology professor.

A quirky mix of avuncular charm and headstrong ambition, Guarente began looking into aging years ago and soon got hooked. By the mid-1990s his lab had become a leader in the field. His investigations into short-lived baker's yeast led to an enzyme called Sir2p that appears to act like a famine sensor: It registers calorie intake and, when it is very low, helps activate the formation of long-living spores—a yeast cell's version of hunkering down in a state of slowed aging. In 1999, Guarente co-founded Elixir Pharmaceuticals, a Cambridge, Mass., biotech that hopes to develop drugs based on his Sir2p work.

Last year one of Guarente's former protégés, David Sinclair, now an associate professor at Harvard Medical School, added a bibulous twist to the story. With collaborators at Biomol International, a Plymouth Meeting, Pa., biotech, he discovered a group of chemicals that stimulate Sir2p. The most potent one turned out to be resveratrol, a compound in red wine. The researchers showed that yeast cells lightly doused with resveratrol are able to divide 70% longer, on average, than normal. (Like us, doddery yeast cells lose the ability to reproduce.) Preliminary experiments suggest that resveratrol slows worm and fruit-fly aging too, the group reported.

Sinclair, a trim, ebullient Australian transplant, has formed a startup—dubbed Sirtris—to develop drugs based on the discovery. "I think resveratrol is mimicking caloric restriction" in yeast, he says. "Now the race is on" to determine whether it does the same thing in mammals, including humans.

The data on that issue are scanty but promising. Sinclair's team has shown that resveratrol boosts the activity of SIRT1, a human version of Sir2p. Meanwhile, Guarente's group has illuminated one of SIRT1's functions: blocking cell suicide. Cells' suicidal tendencies are elicited by damage to their DNA molecules, which occurs as part of normal cell metabolism. When the molecules in a cell are beyond repair, scientists believe, it self-destructs to prevent cancer; deranged DNA can cause tumors. But as we age, or undergo certain kinds of stress, this cellular self-culling

Adult-onset diabetes can be seen as a form of accelerated aging.

Anti-aging drug facts

- **Resveratrol, a compound in red wine, may extend cell life.**
- **Diabetes drugs like metformin may ape the life-extending effects of caloric restriction.**
- **Anti-inflammatories like aspirin and ibuprofen may slow the aging process.**

may veer toward overkill, sapping tissues of regenerative capacity. Experiments by the MIT group suggest that SIRT1, when stimulated by caloric restriction—and possibly by drugs like resveratrol—helps curb the excess.

It doesn't follow, however, that you should guzzle red wine or pop resveratrol pills. Multiple studies suggest that a daily glass of wine might lower your risk of heart disease. But there's currently no compelling evidence that taking resveratrol alone does any good, and over time it might do harm—after all, studies indicate that the compound may quell an anti-cancer mechanism. (Most of the scientific literature, however, suggests that it doesn't raise the risk of cancer.)

So are we stuck waiting around for companies like Elixir and Sirtris to develop drugs that extend our lives? Maybe not. Some scientists, for example, believe that existing diabetes drugs may ape the life-extending effects of caloric restriction. That's not too surprising: Adult-onset diabetes—which is linked to high-calorie diets and obesity—can be seen as a form of accelerated aging. Indeed, a study last year by California's BioMarker Pharmaceuticals found that metformin, a generic drug long used to treat diabetes, boosts certain genes and suppresses others in mice in a way that's strikingly similar to the gene-activity changes induced by CR. And last fall a University of Maryland group observed that an experimental diabetes drug owned by Switzerland's Roche Group, called K-111, mimics many metabolic changes induced by CR in monkeys. But as with resveratrol, the jury is still out—way out—on whether diabetes drugs can safely retard aging.

Then there are the good old anti-inflammatory drugs like aspirin. Over the past decade just about every major disease of aging, from Alzheimer's to cancer, has been linked to low-level inflammation. (See "The Secret Killer," on fortune.com.) That suggests that chronic, low-level inflammation isn't just a risk factor for various diseases—it may be a central part of the aging process. Indeed, in 1998 scientists at the National Institute on Aging showed that 2-year-old mice dosed with an anti-inflammatory called PBN survived, on average, 4% longer than peers not on the drug. That's not bad, given that the mice didn't get the drug until their lives were almost over.

A derivative of PBN is one of the first compounds that the institute is testing in its landmark mouse study on drugs that might slow aging. Another anti-inflammatory on the institute's first-to-try list is aspirin—if it works, we won't have to worry that anti-aging drugs will be too costly for the masses. To ensure the data are reproducible, each of the vetted compounds will be simultaneously tested at the University of Michigan in Ann Arbor, Jackson Laboratory in Bar Harbor, Maine, and the University of Texas Health Science Center in San Antonio.

Don't expect miracles, though. Even if PBN or another drug slows aging in mice, proving it does so in humans probably won't be feasible until scientists can accurately measure how fast a person is aging, letting them demonstrate anti-aging effects without waiting decades for study subjects to expire. (For a rough method to tell how fast you might be aging, see "How Old Am I Really?") And if the effects of caloric restriction are any indication, anti-aging drugs won't boost human life expectancy much past 100 anyway, says Richard A. Miller, a University of Michigan researcher who is already doing a PBN study with mice.

Still, that's a lot better than the current 74.4 and 79.8 life expectancies for U.S. men and women, respectively. And those extra years may well be very good ones. Elderly mice on CR, "our current best guides to what we would expect to see in a 112-year-old CR-facsimile person, are still fairly vigorous and admirably free of degenerative changes," Miller wrote in a 2002 article on life-extension research in *The Milbank Quarterly*, a health policy journal. Thus, anti-aging drugs, he believes, probably won't "prolong the period of late-life suffering but instead delay its appearance by increasing the length of healthy adult life."

That compelling point, however, fails to win over critics of anti-aging research, who have become increasingly strident as the work has moved closer to fruition. The most prominent naysayer is Leon Kass, chairman of President Bush's Council on Bioethics, who has spoken out against the research as threatening to rob life of the meaning that comes from growing old and dying naturally. He has a point: Anti-aging drugs would be profoundly unnatural. But, it might be added, so are life-expectancy boosters like water sanitation, antibiotics, and seatbelts. F