

IN THE LAB

Counting on low calories' benefits

Drastically reducing food intake may not be easy, but it could result in a younger heart and longer life span, a study finds.

By ANDREAS VON BUBNOFF
Special to The Times

FOUR years ago, Joseph Cordell wasn't looking to lose weight. At 5 feet 9 and 165 pounds and exercising regularly, the then 43-year-old divorce lawyer was in pretty good shape.

But he didn't have anything against adding a few years to his life — and so, in 2002, he overhauled his diet. He cut his daily caloric intake from about 3,000 to 1,900. He turned to a diet rich in walnuts, berries, apple peels, broccoli, mountains of salad and lean protein. He says he now weighs 129 pounds and almost never gets sick anymore.

His heart, it appears, is reaping the benefit.

Last month, scientists at the Washington University School of Medicine in St. Louis published a study showing that the hearts of Cordell and 24 others who had been practicing "caloric restriction" were more youthful-looking when viewed by ultrasound than the hearts of people on regular American diets.

The 25 subjects, who had consumed about one-third less calories than most people would normally eat for an average of 6½ years, had heart walls that were more elastic, with ventricles that relaxed more readily to fill with blood.

"The hearts looked 10 to 15 years younger," says Dr. Luigi Fontana, an assistant professor of medicine at the university and principal author of the paper. The scientists now plan to study what restricting calories does to other parts of the body such as arteries, lungs and kidneys.

The findings, published in the *Journal of the American College of Cardiology*, is a promising sign that a science rooted in animal data might help humans extend their life span. Researchers have found that mice and rats fed 30% fewer calories from an early age live

30% longer than those given regular amounts of chow. Such animal findings have inspired a cadre of caloric restriction enthusiasts, Cordell among them, and a Calorie Restriction Society, which has several thousand members.

It's not yet clear whether caloric restriction can also extend maximum life span in humans, but scientists are continuing to investigate the issue. Because most people probably don't have the discipline to drastically reduce their caloric intake for the rest of their lives, research labs and biotech companies meanwhile are looking for drugs that mimic its effects so people could reap the benefits without self-denial.

If caloric restriction prolongs life, a major question is why. Fontana thinks reducing inflammation may be key. Inflammation usually increases with age and induces effects similar to wound healing, which makes tissues stiffer. Fontana's study found reduced blood levels of two inflammation-linked proteins (TNF-alpha and CRP) in the subjects practicing caloric restriction.

Stiffening could also result from simply turning food into energy. That process creates so-called free radicals, reactive oxygen molecules that can damage tissues. Caloric restriction might reduce the accumulation of such radicals because it reduces the intake of food.

Although scientists say the heart study is compelling, they point out that people undergoing caloric restriction may be unusual in ways beyond consuming fewer calories. (Cordell, for example, is a stickler for good nutrition: One of his strategies is to eat only the

Downsides to a restrictive diet

Drastically reducing caloric intake is known to prolong life span in animals and have health effects in humans. But it's not for everyone and may even be dangerous for some. It requires meticulously monitoring caloric intake while making sure you get the full range of nutrients. Some who practice caloric restriction say they are often cold because they have much less body fat and a slower metabolism. Some have a reduced libido. Lowered bone density is also a concern. But it's not necessary to drastically reduce caloric intake to reduce risk for diseases such as stroke, Type 2 diabetes, hypertension and maybe some types of cancer, says Dr. Luigi Fontana of Washington University School of Medicine in St. Louis. "You just need to switch your food choices from junk foods rich in empty calories to nutrient-dense foods." A Mediterranean diet of whole grains, beans, vegetables, fruits, nuts and fish is a good first step, he says.

peel of an apple because it contains more micronutrients.) "It's hard to sort out what's causing what," says Dr. Evan Hadley, director of the geriatrics and clinical gerontology program at the National Institute on Aging in Bethesda, Md.

To help surmount such issues, the National Institute on Aging has initiated a clinical trial that will randomly assign either a caloric restriction diet or a normal diet to 240 people. The trial will follow people on

caloric restriction for two years and examine the health benefits and risks. Recruitment is expected to start in August.

Meanwhile, several research labs and biotech companies are looking for drugs to mimic caloric restriction. GeroScience in Pylesville, Md., is seeking compounds that trick cells into "thinking" they are fed when they aren't. LifeGen Technologies in Madison, Wis., is studying nutrients that can activate certain genes the way caloric restriction does.

Other companies are focusing on drugs that activate proteins known as sirtuins. Sirtuins appear to be key in caloric restriction. Doubling sirtuin dosage in flies and worms extends their life span by 30% to 50%, says MIT researcher Leonard P. Guarente, a co-founder of Elixir Pharmaceuticals of Cambridge, Mass.

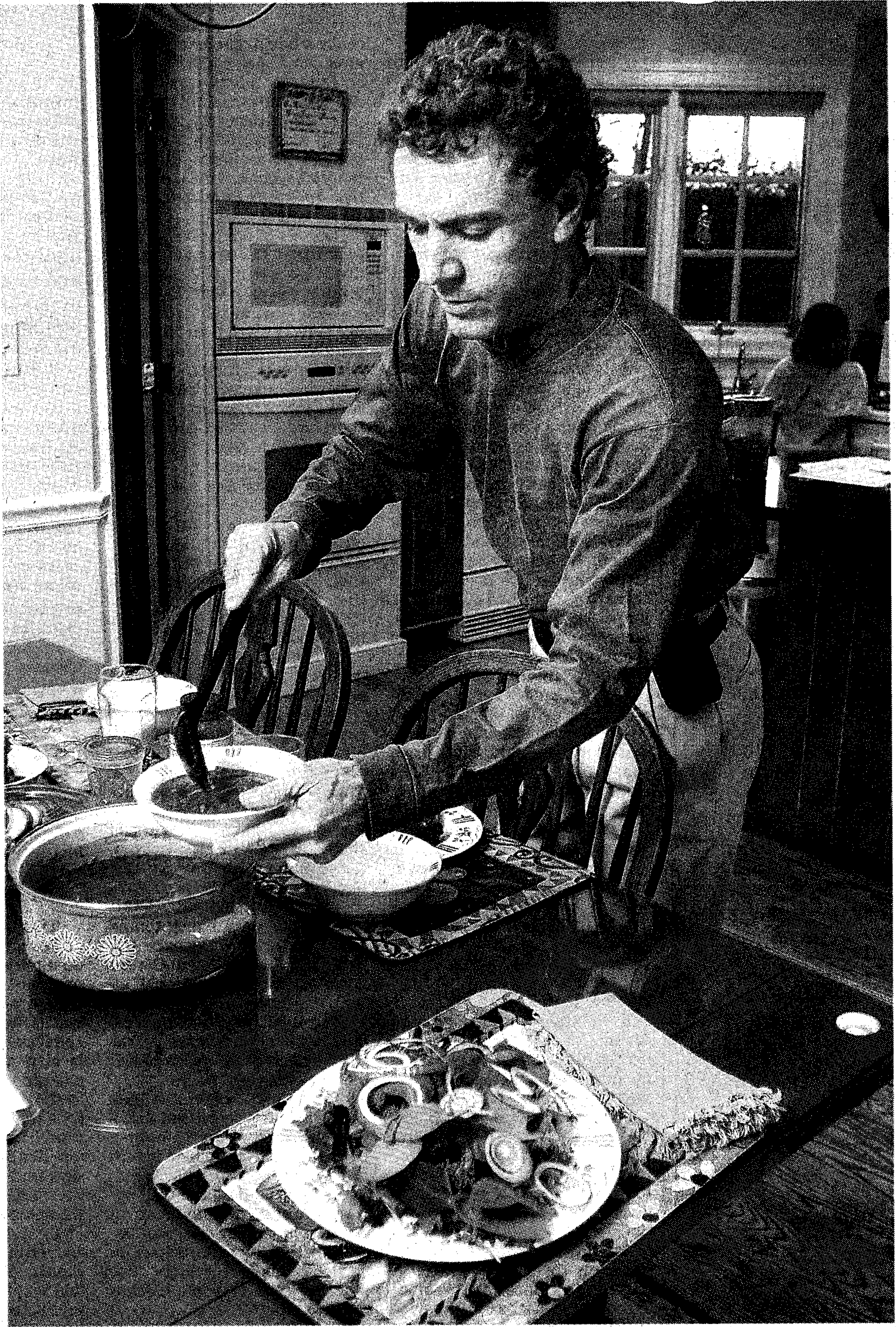
Another Cambridge-based company — Sirtris Pharmaceuticals Inc. — will test the safety of some sirtuin-activating compounds in human clinical trials this year, says co-founder David Sinclair, a Harvard researcher. In 2003, Sinclair's lab identified resveratrol, a sirtuin-activating compound that is found in red wine.

Sinclair is optimistic that the first drugs mimicking caloric restriction will be available in five to 10 years.

But Dr. John Holloszy, a Washington University School of Medicine gerontologist and a co-author on the heart study, is not so sure that proteins such as sirtuins can explain all the effects of caloric restriction.

"I think it's more complicated," he says — only to admit that he takes resveratrol every day, and drinks red wine with dinner.

"It's very nice if it works," he says.



DAVID KENNEDY For The Times

RESTRICTED: *Joseph Cordell's 1,900-calorie daily diet includes lots of greens and lean protein. Cordell now weighs 129 pounds and he and other study participants have hearts that look 10 to 15 years younger.*