ed one-third of the U.S. population—to struggle with therapies that don't really seem to work.

The story of leptin has had as many ups and downs as a chronic dieter's bathroom scale. First discovered in 1994 by a team led by Jeffrey Friedman at The Rockefeller University in New York City, the appetite-suppressing hormone hit the headlines accompanied by pictures of mice that were grossly overweight as a result of leptin gene mutations. Rockefeller University subsequently licensed the human version of leptin to the biotech firm Amgen Inc. of Thousand Oaks, California, for an initial fee of $20 million, and researchers scrambled buoyantly toward the hope of using the hormone as a wonder diet drug.

One sign of trouble came, however, when researchers learned that most obese human patients do not have depleted leptin levels in their bloodstreams. In fact, the heavier the person, the higher the levels. Still, that did not rule out the idea that leptin might work as an obesity therapy. Patients with adult-onset diabetes make insulin, but develop a resistance to the hormone that can sometimes be overcome by insulin injections. Hoping for something similar with leptin, a team led by Mark McCamish at Amgen devised a clinical trial designed to quickly test its safety and efficacy in humans.

Investigators at six sites recruited 54 normal and 73 obese volunteers, who were assigned to receive injections either of a placebo or of leptin at one of four different doses. Obese volunteers were also instructed to diet. After 4 weeks, when the drug appeared to be safe, the obese volunteers were given the choice to go the full 24 weeks planned for the study. Forty-seven completed the study, the rest having dropped out either because of problems with injection sites or noncompliance with the diet or the injections.

At the end of the trial, individuals in the highest dose group had lost a mean weight of 7.1 kilograms as compared to 1.3 kilograms lost by the controls, who were given no drugs. "Our data show that there is not an absolute leptin resistance in this group of [obese] people," says study co-author, nutritionist Steven Heymsfield of St. Luke's-Roosevelt Hospital Center in New York City.

That may be true, say other researchers, including Flier, but a close look at the numbers shows that only patients in the highest two dose groups had significant weight losses compared to those taking the placebo. And even then, several in those groups actually gained weight during the study. "It's looking very much as if there is no real effect except in a subset of patients," Flier says.

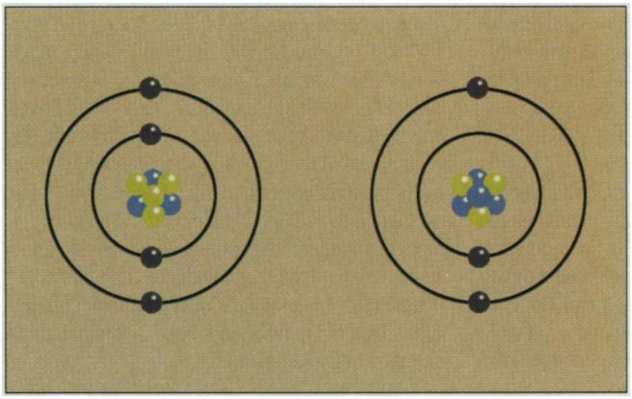
The Amgen team now plans to try to identify exactly what factors made those people more responsive to leptin. If successful, says Heymsfield, "one could screen people beforehand for certain markers and then know the probability of responding would be much higher." He notes that researchers at Addenbrooke Hospital in Cambridge, U.K., reported in the 16 September issue of *The New England Journal of Medicine* that leptin did cure the obesity of a youngster found to have defects in his leptin gene. Such mutations are rare, however, and until researchers learn to identify people with more common types of obesity that respond to leptin, the drug is not likely to appear in pharmacies. **–TRISHA GURA**

Trisha Gura is a writer in Cleveland.

GEOCHEMISTRY

Tweaking the Clock of Radioactive Decay

Certainty, it seems, is on the wane. The sun may rise tomorrow on schedule, and the seasons may pass as they always have. But radioactive decay—the pacemaker of geologic time—can no longer be called precisely "clocklike." Says geochemist Douglas Hammond of the University of Southern California (USC) in Los Angeles: "Everybody always assumes radioactive decay to be totally independent of temperature, pressure, and chemical form. It seems there are some exceptions."



Atomic cannibalism. Beryllium-7 decays by capturing one of its own electrons, transforming a proton into a neutron. Because chemical bonds affect the electrons' behavior, the decay rate of beryllium-7 can depend on its chemical form.

In the 15 September issue of *Earth and Planetary Science Letters*, geochemist Chih-An Huh of the Institute of Earth Sciences of the Academia Sinica in Taipei reports that the decay rate of beryllium-7 varies, depending on its chemical form. Creationists hoping to trim geologic history to biblical proportions will be disappointed—the variations seen so far are much too small, just a percent or so, to affect Earth's overall time scale. Still, the variability in beryllium decay will prompt those who want to trace out fine divisions in the earliest reaches of time to take a close look at their pacemakers.

Theoreticians long ago anticipated some variability of radioactive decay. The decay of beryllium-7, for example, should depend on the density of electrons at the nucleus. That's because it transforms itself into lithium-7 by capturing one of its own electrons, turning one of its protons into a neutron, and emitting a gamma ray. When a change in chemical bonding subtly rearranges the electrons and increases an electron's chance of finding itself at the nucleus, the odds are better that it will be captured and the beryllium will decay.

In the last few years, German researchers have demonstrated the converse of this effect: a surge in the decay of rhenium-187, which emits an electron rather than capturing one. When Fritz Bosch and his colleagues at the Gesellschaft für Schwerionenforschung in Darmstadt, Germany, stripped away all the electrons from rhenium nuclei, something that might happen in a star's harsh interior, its half-life plummeted from 42 billion years to 33 years. But, until now, researchers have detected only tiny variations (or none at all) in the decay rate of beryllium and other atoms under Earth-like conditions.

Undismayed, Huh applied the latest technology to the problem. He used an extremely sensitive but stable gamma ray spectrometer to monitor the decay of beryllium-7 (which has a half-life of about 53.3 days) in the form of the hydrated ion, the hydroxide, and the oxide—chemical combinations common in the environment. Thanks to an unprecedented precision of ±0.01%, he could see that the half-lives of the three forms were 53.69 days, 53.42 days, and 54.23 days, respectively. The 1.5% range is "probably quite real," says geochemist Teh-Lung Ku of USC. "Although the idea has been around quite a while, this time [the researchers] will be able to show it more convincingly."

It remains to be seen how important the effect will be in dating geologic samples. Beryllium-7 is used to gauge the rate of erosion or sediment deposition over weeks to months. Except perhaps in studies aspiring to the highest possible resolution, the decay variability due to chemical form is likely to be swamped by other uncertain-

CREDIT: TRIUMF

ties, says Hammond.

If similar effects turn up in other radioactive clocks that tick over hundreds of millions or even billions of years, however, they would loom large to geochronologists trying to work out the order of closely spaced geologic events in the distant past. Such fine distinctions matter, for example, to researchers who are using the decay of potassium-40 (half-life of 1.25 billion years) to sort out the mass extinction of 250 million years ago (*Science*, 15 May 1998, p. 1007). But, although potassium-40, like beryllium-7, decays by electron capture, its innermost electrons—the ones most likely to be snagged—are more strongly shielded from external effects. The potassium ion has two complete shells of electrons protecting its two innermost electrons, whereas the beryllium ion has none. Thus, researchers expect the effect of chemical form on potassium-40 to be far less than on beryllium-7.

But that won't stop Huh from trying to check the constancy of this clock. Even now, he is counting decay rates of rubidium-83. It has an electronic structure that provides even more shielding than does potassium-40, but its 86-day half-life will make experiments reasonably quick to perform. In a few months, he'll know if ancient days are even a tiny bit closer than we thought.

–RICHARD A. KERR

SCIENTIFIC MISCONDUCT

Shalala Takes Watchdog Office Out of the Hunt

The Department of Health and Human Services (HHS) has decided to downgrade the role of its Office of Research Integrity (ORI) in policing scientific misconduct. The change, in line with a new government-wide policy, strips ORI of the power to conduct investigations and, instead, asks it to teach universities how to prevent misconduct. It will continue to review the results of university investigations and propose sanctions. "ORI now goes into the oversight/recommendation role," says Chris Pascal, acting director of the office, which became notorious a decade ago for its dogged pursuit of allegations against a colleague of Nobelist David Baltimore.

> **"I'm ecstatic about how this has come out."**
> **—Howard Schachman**

Created in 1989 and assigned its present status in 1992, ORI has had responsibility for both investigating misconduct by HHS-funded researchers and imposing sanctions. But the agency's effectiveness was weakened by several instances in which charges against individuals were later abandoned or findings overturned on appeal. The decision by HHS Secretary Donna Shalala essentially adopts a 4-year-old recommendation by a congressionally appointed commission headed by Harvard reproductive biologist Kenneth Ryan (*Science*, 1 December 1995, p. 1431).

The new plan, formulated by an internal review panel headed by Assistant Secretary for Health (ASH) David Satcher, makes HHS dependent primarily on an institution's own investigation. ORI will review the findings and, if necessary, draw up sanctions, which it will send to Satcher as recommendations. "The ASH has no role right now [in that process]," says Pascal. Any additional investigation will be conducted by HHS's inspector-general (IG). Appeals will continue to be heard by a separate HHS panel of experts.

The eight scientist-investigators in ORI's investigative unit will concentrate on oversight and onsite technical assistance, Pascal says. HHS may also provide more direct support: It will soon launch a pilot project to assist institutions unable or unwilling to do their own investigations by offering them help from a consortium of experienced universities. The new scheme is consistent with the approach taken by the National Science Foundation, where the IG handles misconduct investigations and forwards its recommendations to the deputy NSF director. Pascal says ORI has been relying on universities to do most investigations since 1995, when it began to limit the number of cases it pursues. Barbara Mishkin, an attorney at the Washington, D.C., law firm of Hogan & Hartson, who has specialized in misconduct cases, says that ORI has improved its reputation in recent years by training investigators and "being much more selective" about choosing cases.

In announcing the changes at ORI, Shalala also said the department will adopt a newly proposed federal research misconduct definition that would limit misconduct to fabrication, falsification, and plagiarism (*Science*, 15 October, p. 391). University of California, Berkeley, biochemist Howard Schachman, speaking for the Federation of American Societies for Experimental Biology, says the new procedures recognize that universities have learned a lot about handling misconduct cases in the past 10 years. "I'm ecstatic about how this has come out."

–JOCELYN KAISER

SCIENTIFIC MISCONDUCT

Cleared of Misconduct, Geoscientist Sues Critics

Ronald Dorn, a prominent geoscientist at Arizona State University (ASU) in Tempe, has filed suit against the authors of an article, published last year in *Science*, who raised doubts about some of his work. Dorn is charging that statements made in the article, along with other comments by some of the authors, implied that he had doctored rock samples used to date ancient stone carvings.

Hard words. Ronald Dorn says critics of rock-dating technique defamed him.

CREDIT: JEFF HAVIR/ASU

Earlier this month, two investigations concluded that Dorn did not commit scientific misconduct, and last week Dorn finished officially informing the eight scientists that he is suing them for defamation. Both sides are staying mum about the suit, but some observers worry that the litigation could deter potential whistleblowers and chill public discussion of scientific controversies.

The suit is based on a 4-year-old controversy that revolves around a dating technique that Dorn developed in the mid-1980s but abandoned as flawed in 1996. To date stone carvings and geological features such as old shorelines, Dorn used acid to extract microscopic quantities of organic material, including plant remains, from beneath a thin layer of natural varnish on rock surfaces. He then sent the material to an accelerator mass spectrometry (AMS) laboratory to measure the amount of radioactive carbon-14, which decays at a known rate, that was present in the samples. The technique became controversial after it yielded ages for some stone artifacts from the southwestern United States that were several thousand years older than those accepted by many archaeologists.

In 1996, geoscientist Warren Beck of the AMS laboratory at the University of Arizona,