"are valuable to cosmology because they provide additional tests of the age of the universe and its initial composition."

Previously, the only way to study the universe's original makeup was to look at very distant galaxies. Because it takes so long for their light to reach us, we see them as they were soon after they formed, before many generations of stars had forged large amounts of heavy elements. But even the most distant galaxies appear to have been enriched in heavy elements by earlier stars. Also, because these galaxies are so faint, it is hard to discern much detail about the universe's primordial composition in their spectra.

To get a better sample of the early universe, Beers and his colleagues searched our own galaxy's halo, a spherical region of gas, dust, stars, and invisible "dark matter" surrounding the galactic disk, looking for stars whose spectra revealed very small amounts of elements heavier than boron. The astronomers made images of patches of the sky through an instrument called an "objective prism," which smears each star's point of light into a spectrum. "The survey was initiated in 1978, so we are 20 years into it," says Beers, who joined George Preston and Stephen Shectman of the Carnegie Institution's observatories in Pasadena, California, in the first phase of the search.

At first, the astronomers picked likely candidates by eye. Now they scan the plates digitally. "This allows us to find more candidates," says Beers. "Once we have a list of candidates, then we have to go to another telescope and take medium-resolution spectroscopy." By doing so, Beers, Ryan, and Norris identified about 1000 stars that have an iron content 100 times lower than that of the sun—a star that has been preceded by several tens of generations of stars. These stars survived so long because they are small, so they burned their nuclear fuel very slowly, says Ryan.

The old stars aren't completely pristine, however. At least one generation of short-lived stars must have preceded them, because even these oldest stars contain traces of heavy elements—including thorium, which enabled the team to "carbon-date" the stars. Thorium is a radioactive element with a half-life of 14.1 billion years; by measuring its abundance, "we get a direct estimate of the age at which the thorium was formed in presumably a supernova" prior to the star's formation, Beers says. The amount of thorium that has been decayed is determined by comparing it to the amount of europium, a stable element formed during the same nuclear process in the star. According to Beers, John Cowan at the University of Oklahoma, Norman, and Chris Sneden at the University of Texas, Austin, have determined the age of one star to be 13 billion years—close to the age that cosmologists have estimated for the universe as a whole from other data, such as the rate of cosmic expansion.

These stars are already living up to their potential as time capsules. Analyzing the stars' spectra to determine how much lithium their surface layers contain, says Ryan, "allows us to measure how much lithium was produced in the big bang." Beers says the early measurements match predictions based on theorists' picture of the element-forming processes in the primordial fireball.

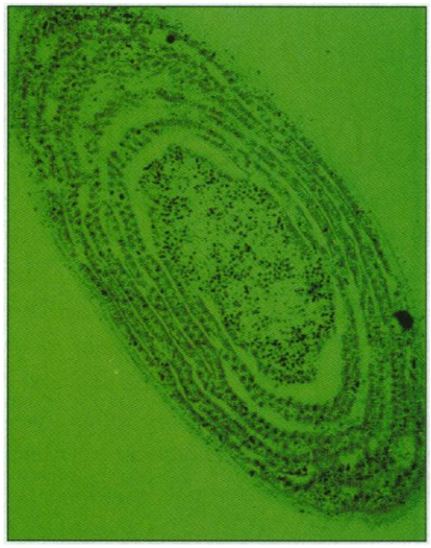
—ALEXANDER HELLEMANS

Alexander Hellemans is a writer in Naples, Italy.

BIOLOGICAL CLOCKS

New Timepiece Has a Familiar Ring

Pendulums, quartz crystals, oscillating atoms—human beings have invented many different ways to keep track of time. Mother Nature, however, seems early on to have hit on one good design for the molecular clocks that govern circadian rhythms and used it repeatedly. The latest evidence for this comes from Masahiro Ishiura and Takao Kondo at Nagoya University in Japan and their colleagues, who on page 1519 describe the workings of the biological clock of the single-celled organisms known as cyanobacteria, or blue-green algae.



ELIZABETH GENTT/VISUALS UNLIMITED

Timeless design. Cyanobacteria such as this one use clocks that work much like ours.

The cyanobacteria clock, which paces 24-hour cycles of activities such as nitrogen fixation and amino acid uptake, is based on the same working principle as are those of fruit flies, mammals, and the bread mold *Neurospora*. At its core is a genetic oscillator, in which a gene produces a protein that accumulates for a while and then feeds back and turns off the gene, causing the protein's concentration to oscillate over a roughly 24-hour cycle. But despite that common scheme, the proteins that make up the cyanobacteria clock are completely different from those of other organisms.

The findings help settle a debate over whether all biological clocks are descended from the same evolutionary ancestor, or whether clocks have arisen more than once during the course of evolution. The cyanobacteria discovery is "the best evidence yet for [clocks'] independent evolution," says Northwestern University clock researcher Joe Takahashi. Keeping track of day-night cycles is apparently so essential, perhaps because it helps organisms prepare for the special physiological needs they will have at various times during the daily cycle, that clocks seem to have arisen multiple times, recreating the same design each time.

To identify the cyanobacterial clock proteins, Kondo and Ishiura began by isolating more than 100 strains with mutations that either abolished or altered the organism's daily activity cycles. The researchers identified the mutated genes by chopping up the cyanobacterial genome and searching for pieces that would restore the normal rhythms when introduced into the mutant bacteria. They found one DNA segment, containing three genes the team called *kaiA*, *-B*, and *-C*—"kai" is Japanese for "cycle"—that could restore all the mutants tested.

All three genes proved essential for the cyanobacterial clock; the Kondo-Ishiura team found that inactivating any one disrupts the organism's rhythms. Other work suggested that the proteins made by the genes are themselves part of the clock mechanism. For one, the researchers found that, as expected for clock components, the activity of the genes oscillates with a 24-hour cycle.

When the team took a closer look at the clock gene activity patterns, their findings suggested a familiar scenario: Early in the day the *kai* genes begin to produce RNA that is translated into protein. Next, KaiA protein apparently turns up the activity of the *kaiB* and *-C* genes. Then after a delay, KaiC seems to step in and turn the genes off. That causes protein levels to fall. As a result, KaiC stops repressing the genes and they come on again. If that model, which fits all the current data, proves true, says Ishiura, that means "regulation of the clock genes is analogous" to the three other known clock systems, in fruit flies, mammals, and *Neurospora*. In fruit flies, for example, the proteins Period and Timeless feed back to turn off their genes.

Many questions remain to be answered about the cyanobacterial clock. Ishiura and his colleagues don't yet know, for example, what causes the delay before KaiC feeds back to turn down its own gene. The ques-

tion is a critical one because the delay before the gene shuts down is what allows protein levels to oscillate with a 24-hour rhythm. The researchers are also on the trail of other proteins that seem to control the *kaiA* gene and help regulate *kaiB* and *-C* as well.

While Ishiura and his colleagues work to fill out the picture, researchers in the field will want to put this new revelation into its evolutionary context. They already knew that the clock proteins of fruit flies and mammals are strikingly similar, making it clear that these clocks evolved from the clock of a common ancestor (*Science*, 5 June, p. 1548). But the *Neurospora* clock has only weak similarities to the animal clocks, raising the possibility that it might have had an independent origin. Researchers disagree about that but say that the cyanobacteria discovery confirms at least two independent origins for clocks.

More may be in the offing. Just this June, researchers got their first glimpse of a plant clock when two teams, one led by John Harada at the University of California, Davis, and the other by Elaine Tobin at UC Los Angeles, identified two different mutations that disrupt the circadian rhythms of the plant *Arabidopsis*. Both affect transcription-control proteins known as MYB proteins, which are unrelated to any known clock proteins. That begins to smell like yet another independent clock, says Steve Kay of The Scripps Research Institute in La Jolla, California.

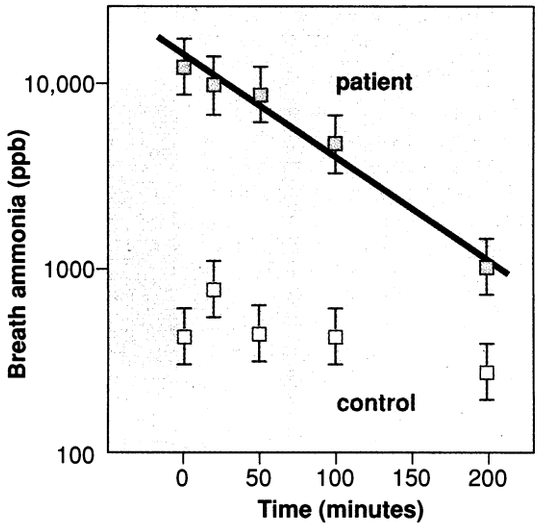
Yet Mother Nature didn't veer far from her tried-and-true system for telling time when she built the *Arabidopsis* clock: The MYB proteins both apparently go back and turn off their own genes. Perhaps, says Kay, feedback on gene transcription has always won out over other possible mechanisms because proteins that regulate their own production are common and therefore readily available to be crafted into clocks. Alternatively, speculates clock researcher Michael Young of Rockefeller University, "maybe this is the only way you can make a clock." **–MARCIA BARINAGA**

MEDICAL TECHNOLOGY

Breathalyzer Device Sniffs for Disease

BOSTON—A whiff of a patient's breath can sometimes be enough to tell a doctor what's wrong. The fishy smell of compounds called amines can indicate kidney problems, while the sweet smell of acetone can mean diabetes. Now two scientists have developed a machine that could turn this practice into a high-tech diagnostic technique, they announced at the American Chemical Society meeting here last week.

In just minutes, the device can analyze a puff of breath for the trace gases that signal diabetes, kidney failure, ulcers, and possibly even cancer. Commercial versions could be available within a few years, providing fast, noninvasive diagnosis. "These are very exciting results," says Michael Henchman, a chemist at Brandeis University in Waltham, Massachusetts, who is not involved in the work. "[This] technique could be as important to medicine as MRI [magnetic resonance imaging]."



SOURCE: D. SMITH/KEELE UNIV.

Telltale breath. Breathalyzer tracks declining ammonia levels—a sign of kidney failure—in a patient undergoing dialysis.

The telltale compounds find their way into the breath when they build up in the blood. As the blood circulates through the lungs, gases in the lungs and blood equilibrate, and the breath carries them out. But developing a diagnostic device that's better than a physician's nose at picking up these wafting fumes has not been easy.

Researchers have tried sniffing out illness, for example, with an instrument known as a gas chromatography–mass spectrometer, or GC-MS. But a GC-MS has trouble dealing with some of the complex mixtures of trace chemicals in the breath. To convert the uncharged organic compounds into charged ions that can be propelled through the mass spectrometer by electric fields, the device bombards the compounds with electrons. The bombardment often breaks down different trace gases into similar smaller components. "It makes it impossible to deconvolute your data" to determine the exact parent compounds, says David Smith, a chemical physicist at Keele University in Staffordshire, United Kingdom.

Two decades ago, when Smith was studying trace gases known to be present in interstellar gas clouds, he developed a gentler way to attach a charge to molecules. His device, known as a selected ion flow tube, or SIFT, reacts compounds in a test sample with carefully selected ions instead of electrons. The reactions change the original compounds only slightly, and each one produces a unique signal in a mass spectrometer.

Three years ago, while working on his technique during a brief stint at the University of Innsbruck in Austria, Smith realized that the same technique might be useful for sorting out the chemicals in breath. Smith and Patrik Spanel, a physicist with the J. Heyrovsky Institute of Physical Chemistry in Prague, Czech Republic, teamed up to adapt the SIFT technique. But they soon faced a new challenge: The ions they intended to react with the trace compounds also reacted with substances that are abundant in breath, such as oxygen, nitrogen, water, and carbon dioxide, which depleted the ions and yielded confusing results. So Smith and Spanel identified a new set of ions—HO_3^+, NO^+, and O_2^+—that don't react readily with the basic ingredients of breath.

Instead, they found that each ion reacted only with certain trace breath components, producing a unique chemical signature for each molecule. And because the SIFT device can generate all three ions simultaneously and feed them into the reaction tube one right after the other, Smith and Spanel were able to obtain complete profiles of all the target compounds from just a single breath. Smith says that he and Spanel have already converted their instrument from a hulking tabletop device to a portable machine that can be wheeled into hospital rooms, and they are currently working to shrink the equipment further.

When Smith and Spanel tested their instrument on patients with various disorders, the results jumped out. Patients with kidney failure, for example, showed levels of ammonia more than 10 times higher than those in controls, because of the waste compounds in their blood. "It essentially delivers an instantaneous diagnosis," says Henchman. The device enabled researchers to watch those levels fall to normal as the patients received dialysis treatment (see graph).

Smith also reported that the machine can gauge a subject's stress level by tracking isoprene, as well as track markers for diabetes and ulcers. Preliminary data even suggest that it could detect hydrocarbons (he declined to say which ones) associated with bladder and prostate cancer. In addition, Smith believes the new machine will prove to have a versatile nose for trouble and could monitor air quality and food freshness as well as disease. **–ROBERT F. SERVICE**