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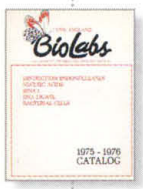

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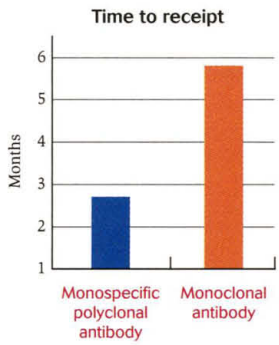

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Science

Volume 298 20 December 2002 Number 5602

2312
Behind the smallpox vaccination decision

NEWS

NEWS OF THE WEEK

NEWS FOCUS

2341
Clues to Earth's early atmosphere

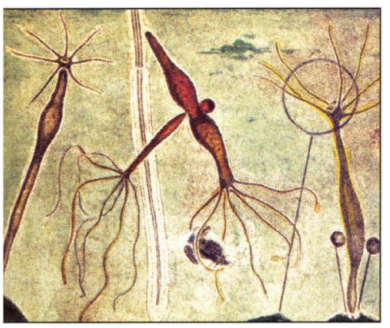
SCIENCE'S COMPASS

HISTORICAL ESSAY

POLICY FORUM

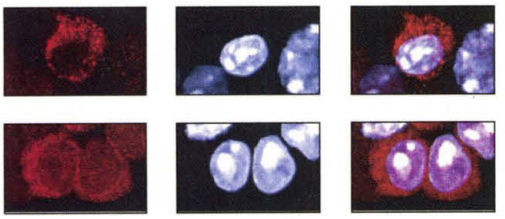
BOOKS *ET AL.*

2333
Science origins of abstract art



PERSPECTIVES

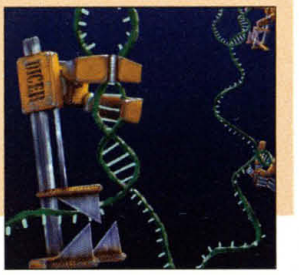
REVIEW



2388

Kinesin acts with ACT for sperm development

Breakthrough of the Year: New Roles for RNAs



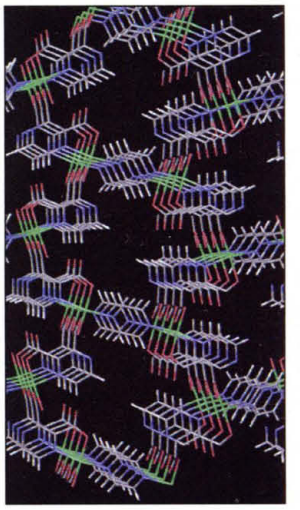
COVER 2296

Researchers are discovering that small RNA molecules play a surprising variety of key roles in cells. They can inhibit translation of messenger RNA into protein, cause degradation of other messenger RNAs, and even initiate complete silencing of gene expression from the genome. See the Breakthrough of the Year special section and the accompanying Editorial. [Illustration: Cameron Slayden]

RESEARCH

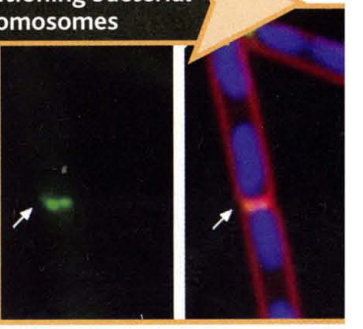
2358

Hosting lines of oxygen molecules



New on *Science* Express

Positioning bacterial chromosomes



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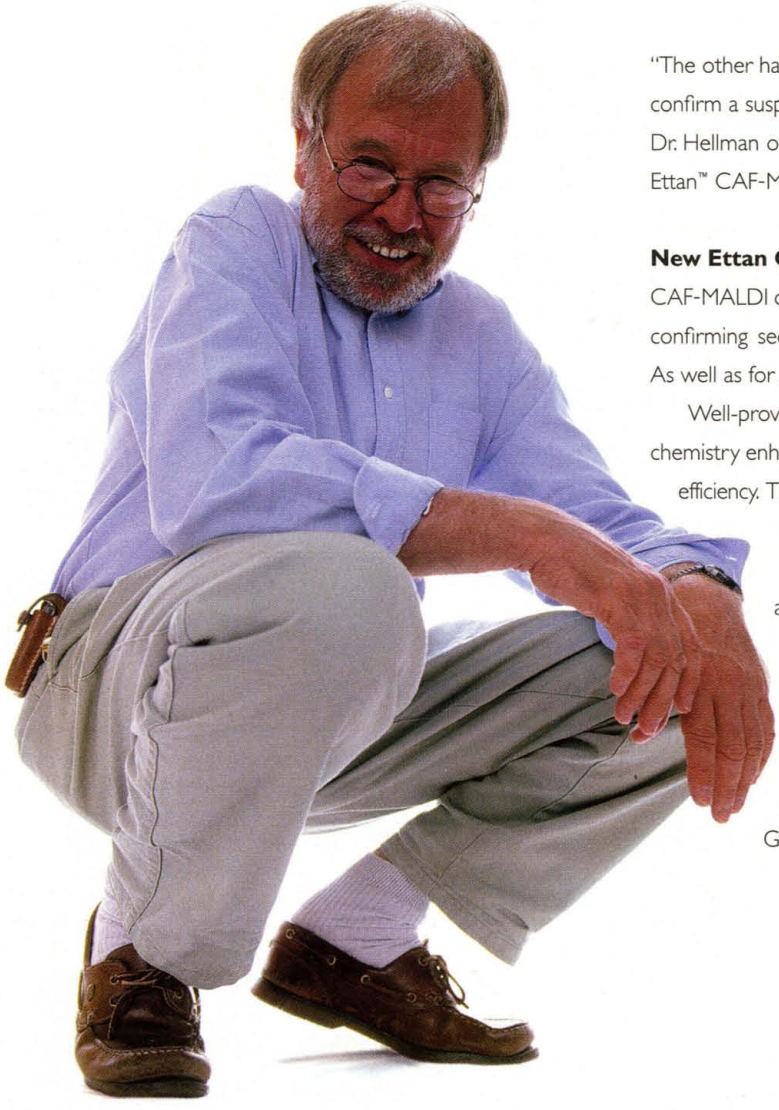

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CONTENT HIGHLIGHTS AS OF 20 DECEMBER 2002

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Production of α1,3-Galactosyltransferase–Deficient Pigs C. J. Phelps *et al.*

A selection procedure has been used to generate pigs lacking α1,3-galactosyltransferase, which represent a resource for xenotransplantation.

RacA, a Bacterial Protein that Anchors Chromosomes to the Cell Poles S. Ben-Yehuda, D. Z. Rudner, R. Losick

A structural scaffold for chromosome partitioning has been identified in sporulating *Bacillus subtilis*.

TECHNICAL COMMENTS

Is Schizophrenia Linked to Chromosome 1q?

Levinson *et al.* (Reports, 26 April 2002, p. 739) conducted a multicenter study of 779 families with schizophrenia and found no evidence of genetic linkage to chromosome 1q—contrary to several previous reports implicating this region in the disease. In separate comments, Macgregor *et al.* and Bassett *et al.* assert that locus heterogeniety can explain the divergent results and that failure to replicate linkage may indicate more about the relative merit of different study designs than about the genetics of schizophrenia. Levinson *et al.* respond that although schizophrenia susceptibility genes may exist on 1q, classical heterogeneity cannot explain a substantial portion of disease cases. They further emphasize the importance of large, multicenter linkage studies to help confirm and localize the multiple interacting loci likely to be involved in schizophrenia.

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/298/5602/2277a

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GERMANY: Budget Woes E. von Ruschkowski

Next Wave investigates the effect of a frozen education and research budget on Germany's scientists.

US: Are Postdocs Employees? Postdocs and the Law, Part 3 L. Haak

Institutions and funding agencies classify postdocs in any number of ways, but what does case law say about employee status for postdocs?

SINGAPORE: Juggling Work and Study J. Chua

Holding on to a professional dream can be difficult, particularly when balancing a full-time job with part-time pursuit of a graduate degree.

UK: Yours Transferredly—Turn Your Data into a T-shirt P. H. Dee

Being spontaneous does not come naturally to most scientists—but the run up to the holidays is a good time to try.

NETHERLANDS: A Heart for Science M. van der Putten

Minority mentors can inspire the next generation of minority scientists, says Turkish-born cardiac researcher Arif Elvan.

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PERSPECTIVE: Wake Up and Smell the Maillard Reaction V. M. Monnier and M. E. Obrenovich

Do processed foods promote aging and age-related disease?

REVIEW: Lipid Peroxidation and the Aging Process D. Praticò

Damaged lipids might hasten decline.

ORIENTATION ARTICLE: The Burden of Pain on the Shoulders of Aging M. Beckman

When growing old hurts.

NEWS FOCUS: Rookie Rising I. Chen

Matt Kaeberlein went from first-year grad student to biotech exec in just 4 years.

NOTEWORTHY THIS WEEK: Paper Chase M. Leslie

Novel database charts path through calorie-restriction literature.

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THIS WEEK IN Science

edited by Phil Szuromi

Two Looks at the LDL Receptor

The low-density lipoprotein receptor (LDL-R) plays a key role in cholesterol homeostasis, and mutations in its gene can lead to familial hypercholesterolemia. The receptor binds LDL at neutral pH; after internalization, it releases LDL at low endosomal pH. The lipoprotein is subsequently degraded while the receptor is recycled. Rudenko *et al.* (p. 2353; see the Perspective by Innerarity) have determined the structure at 3.7 angstrom resolution of the extracellular portion of LDL-R at pH 5.3. The ligand binding domain folds back as an arc over the epidermal growth factor (EGF) precursor homology domain to facilitate an intramolecular interaction with features that are consistent with reversible pH-regulated binding. This interaction likely occurs in the endosomes to displace bound LDL. Multidomain proteins like LDL-R are thought to fold domain by domain from the amino- to the carboxyl-terminus as they are translated. Jansens *et al.* (p. 2401) examined the folding of LDL-R by analyzing the production of conformation-specific epitopes and by looking at the pattern of disulfide bond formation in nascent molecules. They found instead that each domain folded separately during translation and that different domains appeared to fold posttranslationally and out of the expected sequence.

A Mixed Message

An 18-year time series of the ocean carbon cycle near Bermuda reported by Gruber *et al.* (p. 2374; see the Perspective by Quay) shows that changes in sea surface temperature and the depth of the winter mixed-layer cause CO_2 uptake there to be highly variable. Because these physical properties are closely associated with the North Atlantic Oscillation, the authors suggest that the entire subtropical North Atlantic Ocean carbon cycle may fluctuate annually by as much as 50%.

Reducing Schemes

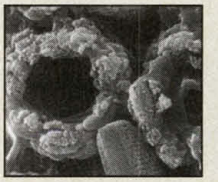
Geological evidence suggests that Earth's early atmosphere had little free oxygen, but direct evidence of oxygen content during Earth's history has been unavailable. Two reports take advantage of the better record of sulfur isotope values for much of the Precambrian to infer the abundance of oxygen and the sulfur chemistry of the early Earth (see the Perspective by Wiechert). Isotopic fractionation is normally mass dependent, but exceptions are known, including the mass-independent photochemical fractionation of sulfur that occurs today in the upper atmosphere where ozone is absent. For sulfur, evidence for mass-independent effects that reflect a paucity of atmospheric oxygen has been found in Archean crustal rocks. Farquhar *et al.* (p. 2369) now report evidence of mass-independent isotope effects in sulfide inclusions in ancient diamonds, which are derived from deep in Earth's mantle. These data provide direct evidence that these diamonds were sampling material that reflected processes in Earth's atmosphere and had been subducted into the mantle during the Archean. Archean sulfide rocks are much less depleted than are modern sulfides in ^{34}S, an isotope that reflects bacterial processing. In culture experiments, Habicht *et al.* (p. 2372) show that the isotope data limit Archean ocean sulfate concentrations to 200 micromolar or less, considerably lower than previously thought. These data also imply that the atmosphere had little free oxygen but an abundance of the greenhouse-gas methane produced through the action of more prevalent methanogens.

2366 Stable Semiconducting Analogs of Zeolites

The microporous zeolites oxides are generally insulators, but analogous compounds based on sulfur and selenium that use cations such as In, Ge, and Sn as the central atom instead of Si or Al are semiconductors that could have unusual electronic and photophysical properties. However, nanoporous analogs have often exhibited poor thermal stability that limits their use in applications such as catalysis. Zheng *et al.* (p. 2366) found that they could achieve high thermal stability (up to at least 380°C) in several different compounds by mixing tetravalent and trivalent

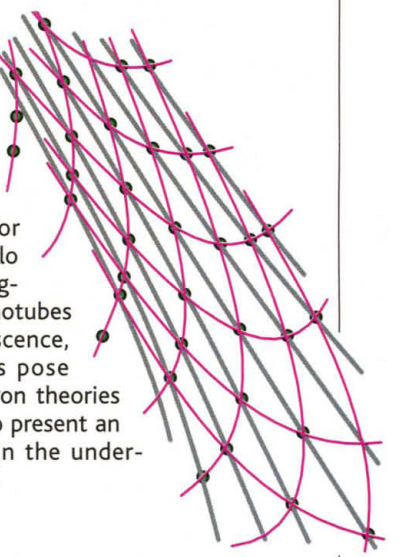
And in Brevia ...

Bacterial microfossils in carbonate rocks, similar in many respects to modern cyanobacteria, are shown by Kazmierczak and Altermann (p. 2351) to be 2.5 billion years old.



Name That Tube

Single-walled carbon nanotubes can be described by an (*n*,*m*) naming convention that specifies different angles for rolling up a graphene sheet into a tube. The properties of the tubes change for each (*n*,*m*) combination, and Bachilo *et al.* (p. 2361) have identified a signature for the semiconducting nanotubes based on their absorption, fluorescence, and Raman spectra. The authors pose questions about current one-electron theories of nanotube-excited states and also present an analytical method that may aid in the understanding of nanotube synthesis.



Where We Come From

Understanding the distribution of genetic variation among human populations, where a population can be a cultural or geographic stratification, is important for studies ranging from evolution to clinical medicine. Rosenberg *et al.* (p. 2381; see the Perspective by King and Motulsky) used short tandem repeat poly-

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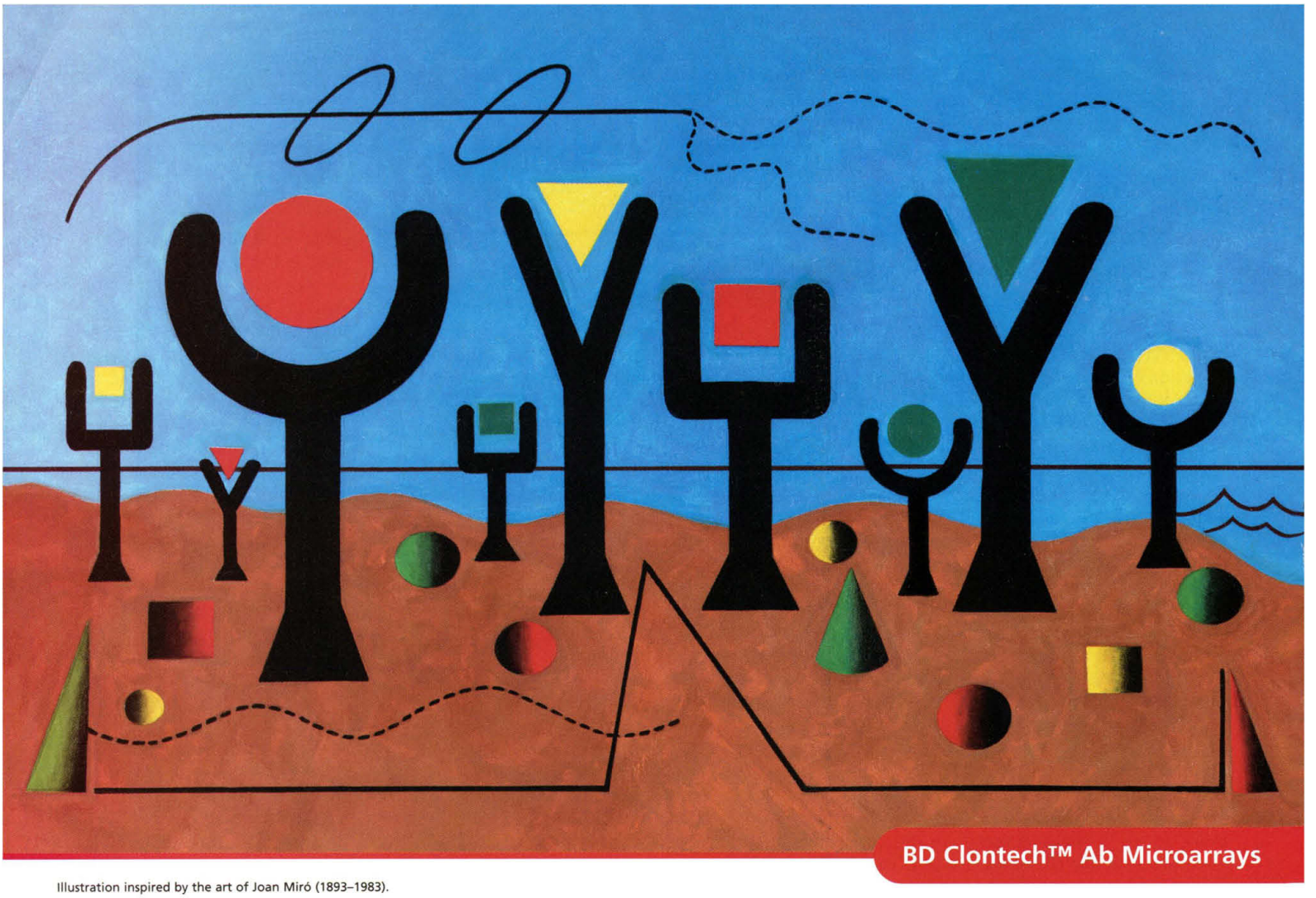

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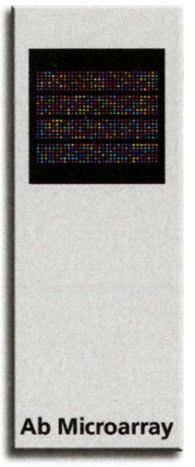

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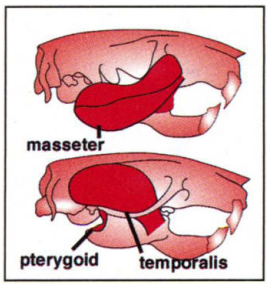
morphisms to characterize 1056 individuals from all continents. Only a small amount of the variation resulted from differences between populations; more than 90% of the variation was between individuals within given populations. Nevertheless, the authors developed an algorithm for cluster analysis that could assign nearly all individuals studied to a major geographic grouping without other information.



CREDIT: LU *ET AL.*

Muscles That Save Face

The muscles of the head and the trunk in vertebrates are specified by different genetic pathways, but much more has been known about the transcription factors involved in skeletal muscle development than those that control head muscle formation. Lu *et al.* (p. 2378) now show that when the genes for the transcription factors MyoR and capsulin are inactivated in mice, specific subsets of face muscles are eliminated.

Gas-Driven Transcriptional Regulation

Gene expression in mammalian cells is controlled by environmental and metabolic cues, but little is known about the molecular mechanisms that sense and respond to these cues. Dioum *et al.* (p. 2385; see the Perspective by Boehning and Snyder and the 22 November Prize Essay by Rutter) have discovered one intriguing mechanism in a study of NPAS2 (neuronal PAS domain protein 2), a transcription factor implicated in the control of circadian rhythms. NPAS2 was shown to bind heme as a prosthetic group, and the heme, in turn, was shown to function as a gas-regulated sensor. In experiments with purified proteins, carbon monoxide (CO) was identified as a candidate ligand for this sensor. Exposure to CO inhibited the dimerization of NPAS2 with BMAL1, the protein that confers the transcription factor with DNA binding activity.

Transcriptional Regulation via ACTive Transport

Molecules called kinesins are critical for the movement of chromosomes, organelles, and messenger RNAs within cells. Macho *et al.* (p. 2388) now show that the testis-specific kinesin KIF17b can function in the transport of the coactivator ACT and affect transcriptional activity. ACT is a coactivator of CREM-mediated transcription in mammalian spermatids. KIF17b acts as a dose-dependent inhibitor of ACT-dependent transcription by excluding ACT from the nucleus. This work begins to address the molecular mechanism by which germ-cell gene expression is regulated.

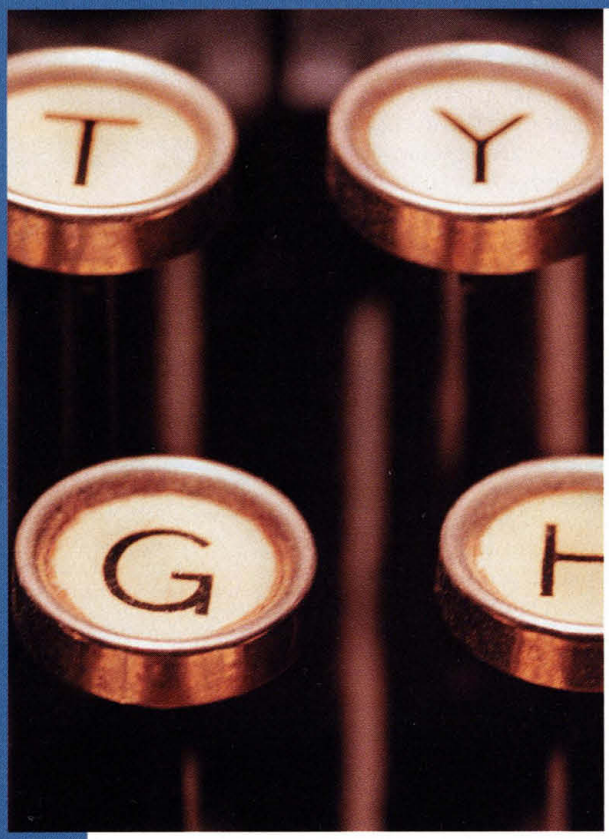
Coordinate Metabolism? Yes, Sir2!

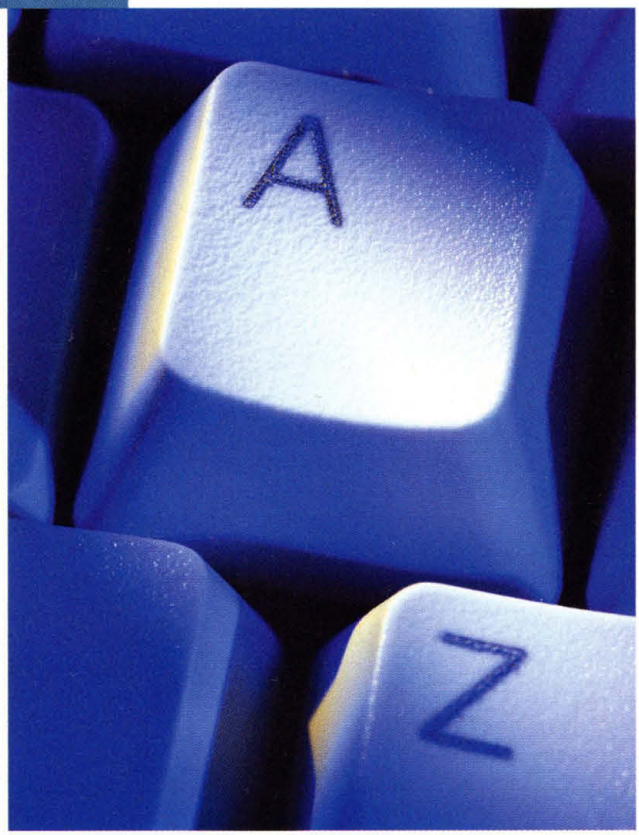
The highly conserved Sir2 family of proteins are involved in regulating chromosome stability and cell aging in eukaryotes, as well as gene silencing in both eukaryotes and archea. Sir2 has nicotinamide adenine dinucleotide (NAD^+)–dependent deacetylase activity and its substrates include histones and the tumor suppressor p53. Starai *et al.* (p. 2390) show that the *Salmonella enterica* acetyl-CoA synthetase is turned off by post-translational acetylation of a lysine residue in the active site. The Sir2 homolog CobB switches on the activity of acetyl-CoA synthetase by deacetylating this residue. The conservation of these proteins suggests that lysine acetylation is a common regulatory mechanism in prokaryotes and eukaryotes, in the latter case providing a link between the acetylation of histones and the physiological state of the cell.

Additional Early Steps in Photosynthesis

Carotenoids increase the range of wavelengths that can be used for photosynthesis by absorbing light energy and efficiently transferring it to chlorophyll. Carotenoid photophysics was classically interpreted in terms of two low-lying excited singlet states, S_2 and S_1. However, recent theoretical and experimental studies suggested that an intermediate excited state might be involved in energy transfer. Cerullo *et al.* (p. 2395) used ultrafast spectroscopy to identify directly a short-lived excited state (S_x) that mediates the internal conversion between the S_2 and S_1 states.

Evolve





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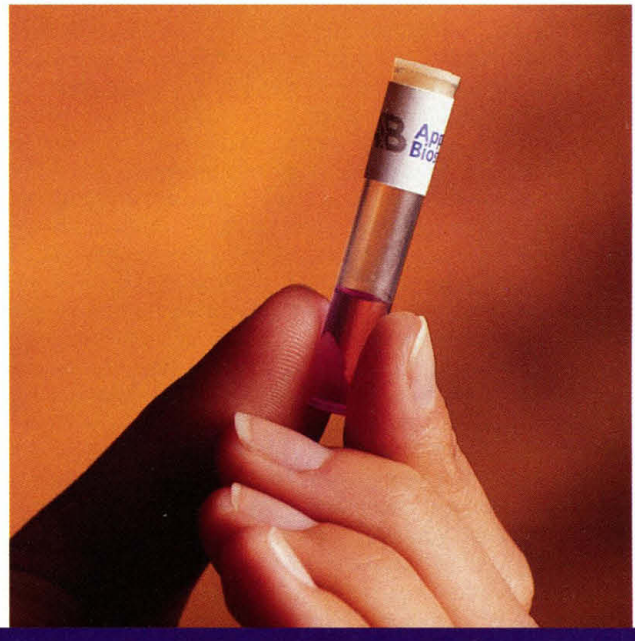

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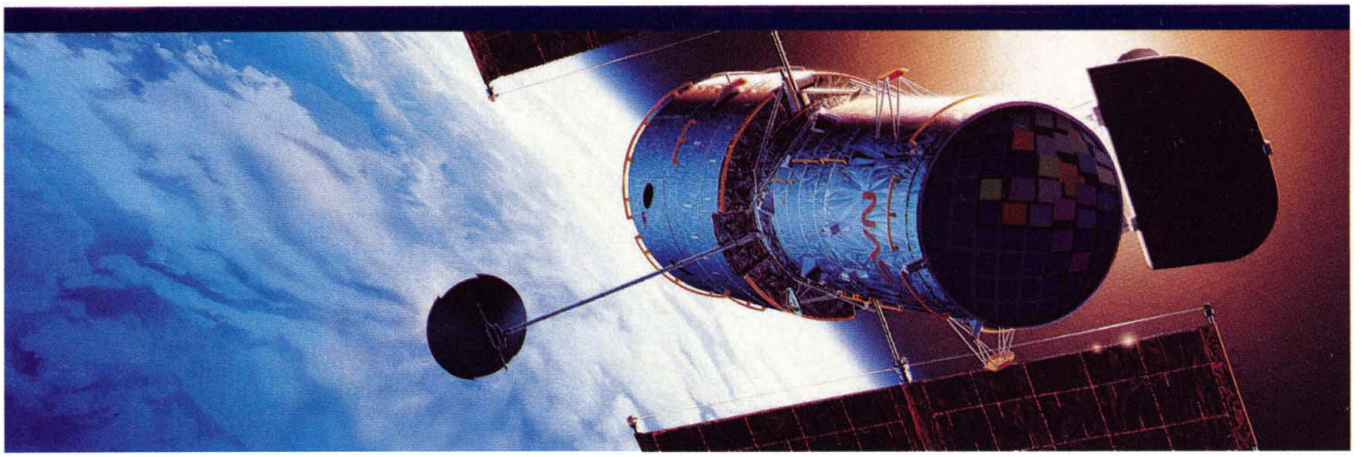

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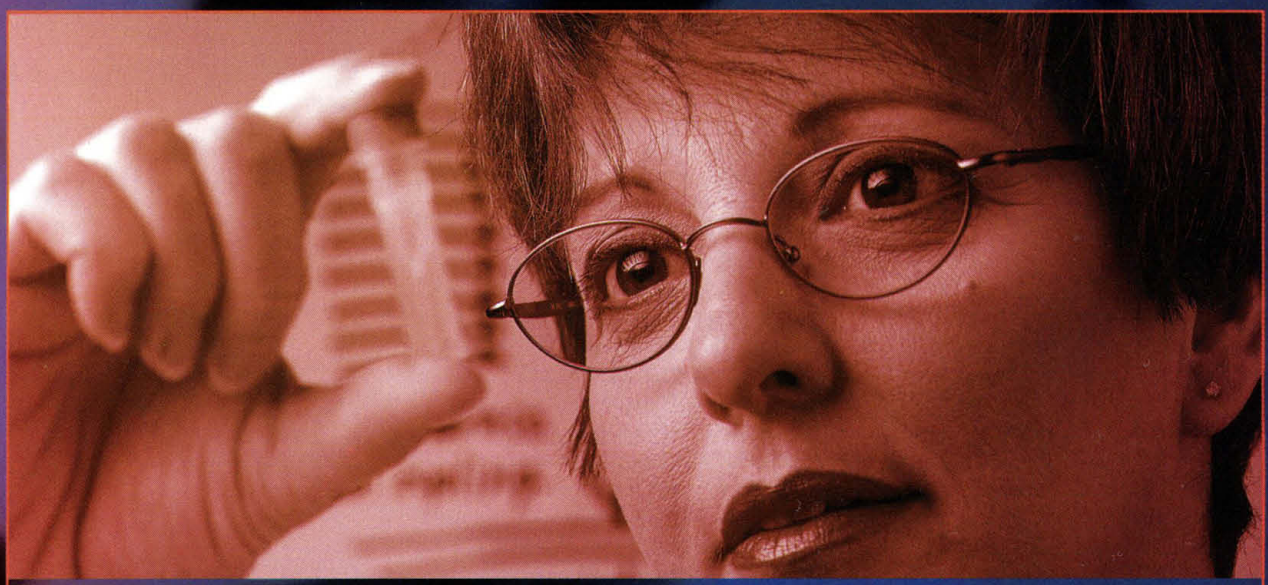

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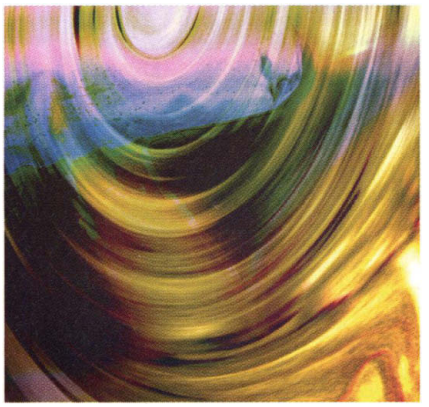

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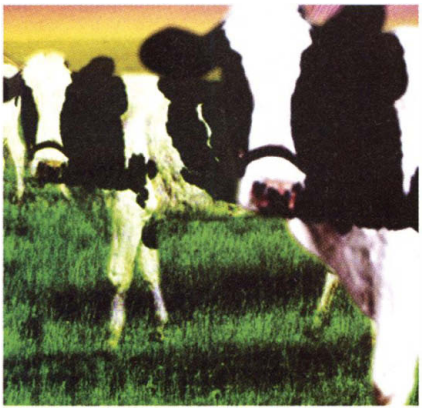

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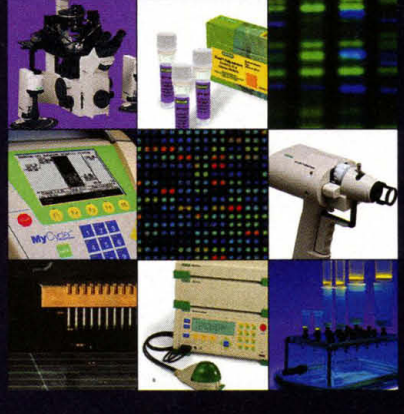

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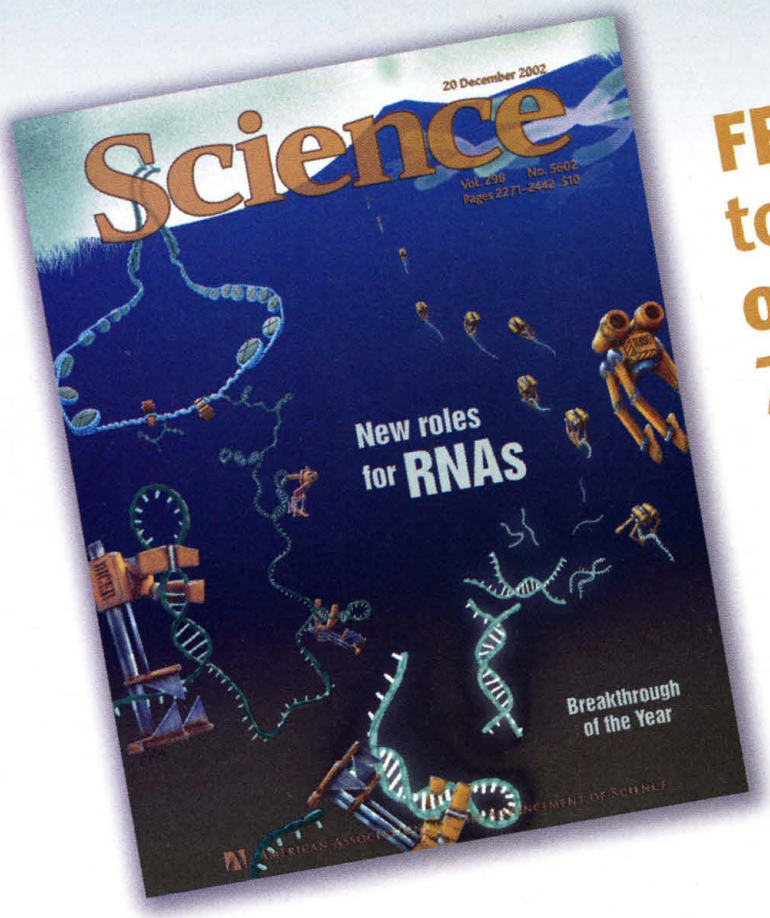

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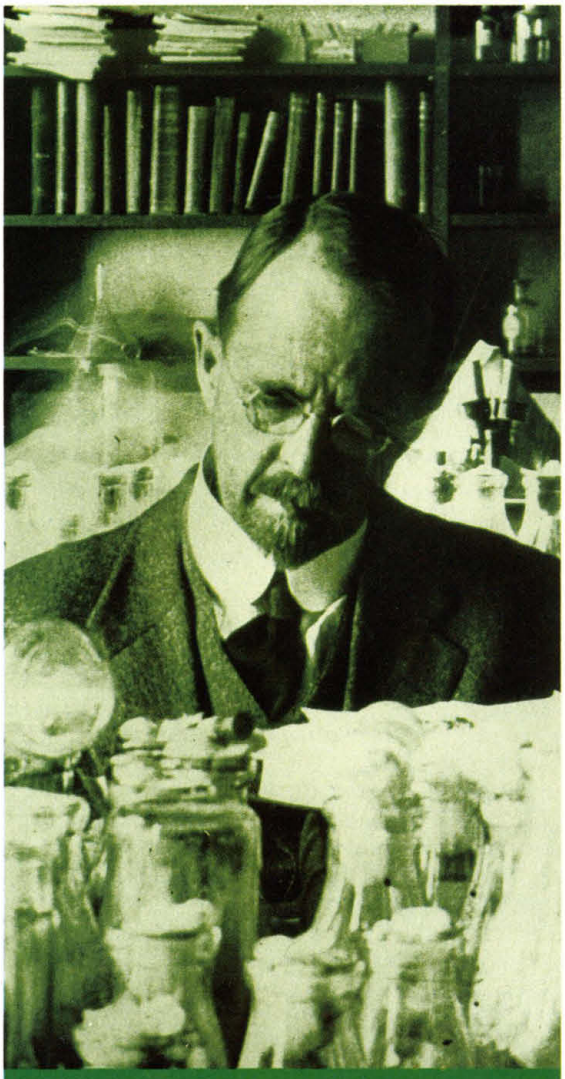

Thomas Hunt Morgan in the lab, 1922

Photo by A. F. Huettner, Courtesy of the Archives, California Institute of Technology

The lowly fruit fly became a noble harbinger of scientific discovery in 1910, when *Science* published Thomas Hunt Morgan's pioneering genetic experiments with *Drosophila*. His work helped determine how heredity and genetics influenced evolution, and he won the Nobel Prize in 1933.

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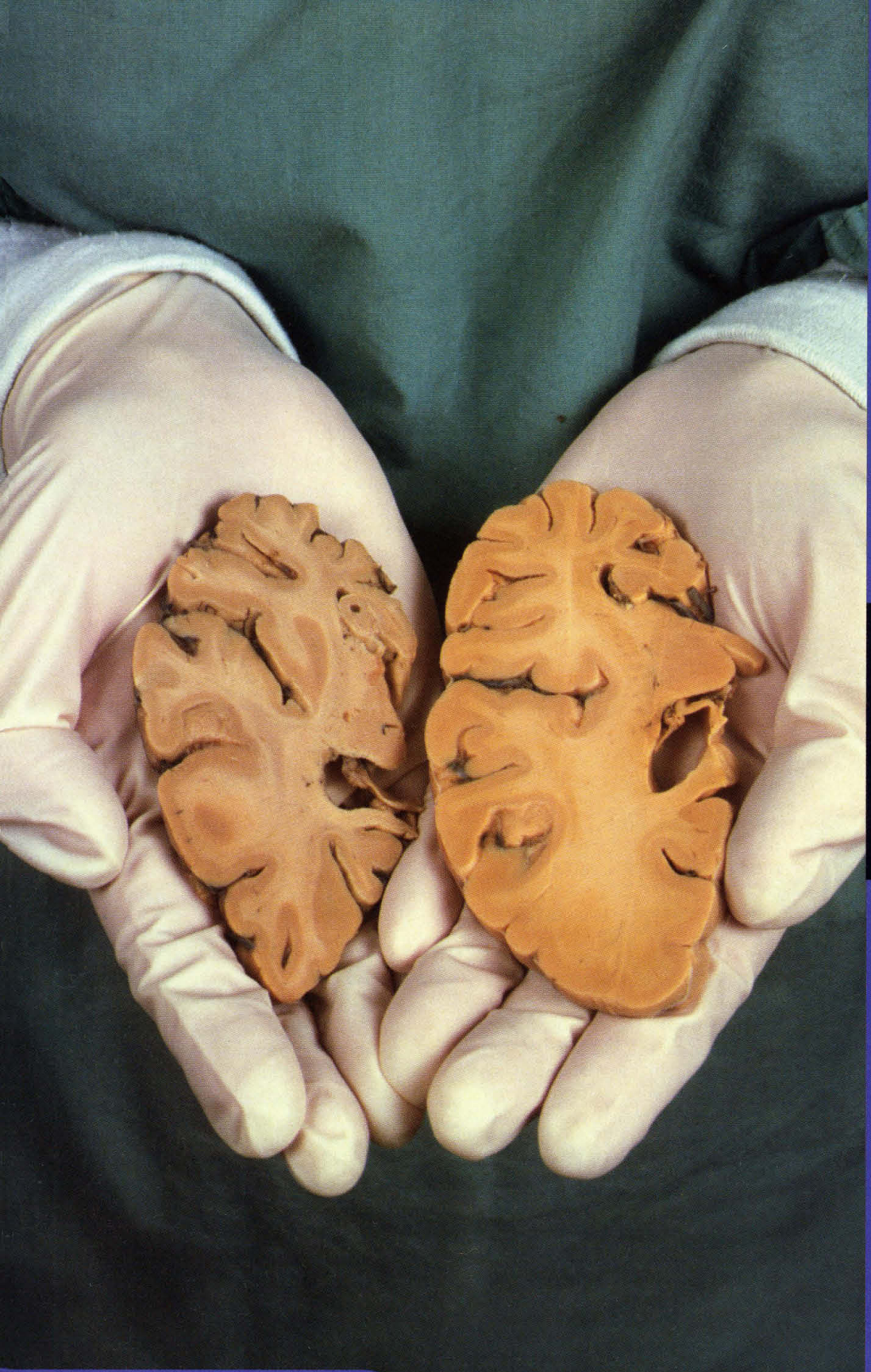

The long-term toll. Over many years, Alzheimer's disease (AD) kills so many nerve cells that the brain shrinks. Compare a slice from the brain of someone with AD (left) with a corresponding slice from a normal brain (right). [Credit: Simon Fraser / MRC Unit, Newcastle General Hospital / Science Photo Library]

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