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**Figure 1:**

Figure Legend: Fractionation of end labeled DNA markers on 3 mm thick 0.8% agarose by the VAGE apparatus and transfer to Duralon™ EY™ membranes using the PosiBlot pressure bloter.

A. Ethidium stained gel showing high resolution.
B. Same gel after pressure blotting.
C. Autoradiogram of membrane after pressure transfer.
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NEWS & COMMENT

DNA Fingerprinting: Academy Reports 300
Why Watson Quit as Project Head 301
Was Argonne Whistleblower Really Blowing Smoke? 303
Kinsey Institute Director Sues Indiana University 304
New Clinical Trial Planned 305
Physics Facilities Come Under Fire: DOE Bites the Bullet • Whacking at the SSC 305

RESEARCH NEWS

The Ascent of Odorless Chemistry 306
Anthropologists Bet on Their Latest Data in Las Vegas 308
New Methods Make Mid-Sized Molecules Easier to Solve 309
Chemists Vie to Make a Better Taxol 311
Quasars: Ablaze With Gamma Rays 311

SPECIAL SECTION

Large Scale Measurements

NEWS REPORTS

Turning a Keen Eye on the Stars • A Military Navigation System Might Probe Lofty "Weather" • Cosmologists Search the Universe For a Dubious Panacea

ARTICLES

The Hubble Constant 321
J. P. Huchra

LIGO: The Laser Interferometer Gravitational-Wave Observatory

Gravitational-Wave Observatories


Global Tectonics and Space Geodesy

R. G. Gordon and S. Stein

Measured Trends in Stratospheric Ozene

R. Stolarski, R. Bojkov, L. Bishop, C. Zerefos, J. Staehelin, J. Jawodny

DEPARTMENTS

THIS WEEK IN SCIENCE 287
EDITORIAL 289
LETTERS 292
The Insanity Defense and Mental Illness: W. T. Carpenter and J. R. Rapoport; M. Sabshin, H. A. Pincus, W. Davis; P. R. Marques; B. J. Ballermann; D. E. Koshland, Jr. • Effects of Low Levels of Lead Exposure: J. F. Rosen; H. L. Needleman

SCIENCESCOPE 299
Epidemiologists head down to the farm; etc.

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George M. Whitesides
Owen N. Witte
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377 Bacterial nucleoid condensation

SCIENCE • VOL. 256 • 17 APRIL 1992
Illustration of one site in the proposed Laser Interferometer Gravitational-Wave Observatory (LIGO). The LIGO facilities will consist of two such interferometers located at widely dispersed sites; scientists hope LIGO will be able to detect gravitational waves emanating from collisions of black holes and neutron stars. See page 325. A special section in this issue of Science focuses on large scale measurements; see the Editorial and pages 316 to 349. [Illustration: Ruth Sofair Ketler]

**RESEARCH ARTICLE**

Allosteric Effects of Nucleotide Cofactors on Escherichia coli Rep Helicase–DNA Binding I. Wong and T. M. Lohman

**REPORTS**


**ARTICLE**

Reciprocal Regulation of Adipogenesis by Myc and C/EBPα S. O. Freytag and T. J. Geddes Cell Cycle–Regulated Binding of c-Abl Tyrosine Kinase to DNA E. T. Kipreos and J. Y. J. Wang Appearance of Water Channels in Xenopus Oocytes Expressing Red Cell CHIP28 Protein G. M. Preston, T. P. Carroll, W. B. Guggino, P. Agre

333 Wide regions of deformation associated with plate boundaries

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During replication double-stranded DNA unwinds to form segments of single-stranded DNA through the action of helicase enzymes. Wong and Lohman (p. 350) explored the mechanistic details of the Escherichia coli Rep helicase by comparing the energetics of DNA binding and DNA-induced Rep dimerization for different nucleotide cofactors, ADP (adenosine diphosphate) and AMP(NH)P, a non-hydrolyzable analog of adenosine triphosphate (ATP). On the basis of these results they propose a rolling model for the unwinding of duplex DNA in which binding of ATP moves the helicase along the DNA; subsequent hydrolysis unwinds several base pairs.

### A family affair
Some protein families contain transcription factors that are structurally related. However, each family member may respond to different regulatory signals and function in distinct ways in different cell types. The C/EBP family of proteins belongs to the bZip class of transcription factors. C/EBPα has been shown to function in the adipogenesis of 3T3-L1 cells. The sequence-specific DNA binding protein Myc is involved in the control of cellular proliferation and differentiation. Freytag and Geddes (p. 379) show that expression of Myc in 3T3-L1 adipoblasts inhibits the induction of adipogenesis (formation of fat cells) by C/EBPα. Changes in intracellular calcium levels can result in the activation of specific genes. Wegner et al. (p. 370) show that another member of the C/EBP family, C/EBPβ, is phosphorylated in pituitary cells in response to an increase in intracellular calcium. The calcium-calmodulin-dependent protein kinase II phosphorylates C/EBPβ in vitro at Ser276. Mutation of this site in C/EBPβ prohibits calcium-regulated stimulation of a reporter gene containing C/EBPβ binding sites.

### Chlamydia chromosome
During the biphasic life cycle of Chlamydia trachomatis, a sexually transmitted parasite that can cause blindness, the chromosome undergoes organizational changes that appear to be regulated by the expression of Hc1, a protein related to eu karyotic histones. In its extracellular phase, the chromosome is unusually condensed for a prokaryote and does not undergo transcription, but after entering host cells the chromosome is loosely organized and transcription occurs. Barry et al. (p. 377) expressed the gene for Hc1 in Escherichia coli and observed by microscopy the formation of a condensed nucleoid structure that is similar to that in Chlamydia.

### Altered states
One way to increase both the specificity and the repertoire of genes whose expression can be regulated is through interaction among distinct transcription factors. Another means of expanding regulatory possibilities is to generate functionally distinct forms of transcription factors through alternate splicing. Narayanan et al. (p. 367) identified a naturally occurring variant of p65, one of the two constituent proteins of the transcription factor NF-κB, that contains a deletion in the transcriptional activation domain (p65Δ). A member of the Rel family of proteins, p65 participates in the transcriptional regulation of viral and cellular genes. Expression of p65Δ but not p65 in Rat-1 fibroblasts resulted in focus formation in culture and tumor formation by injection of transformed Rat-1 cells into nude mice. In vitro assays showed that p65Δ interfered with DNA binding by p65. Myc is a transcription factor that is involved in the control of cell proliferation, and its binding to DNA is enhanced by the protein Max. Makela et al. (p. 373) identified an alternate form of Max (ΔMax) that can still bind to DNA in a complex with Myc, but lacks a nuclear localization signal. Expression of Max in rat embryo fibroblasts suppressed transformation, while ΔMax enhanced this process.
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Circle No. 12 on Readers' Service Card
The Insanity Defense and Mental Illness

Daniel E. Koshland, Jr.'s editorial “Elephants, monstrosities, and the law” (14 Feb., p. 777) is ill-informed criticism of psychiatry, mental illness, and the insanity defense. Koshland echoes the public misconception that a successful insanity defense leads to early release on the basis of psychiatric testimony of cure. In fact, the length of hospitalization after a successful insanity defense may be longer than the time served in prison by those convicted of similar crimes. The number of subsequent criminal acts is greater for the convicted criminal released from prison than for the insanity acquitted released from a mental hospital (1). Koshland adds the voice of Science to the oft-stated claim that public safety is placed at risk by the insanity defense, when data and scholarly opinion are to the contrary. The insanity defense is not often raised, in part because defendants fear the consequence of success (indeterminant involuntary hospitalization). The insanity defense is raised in about 1% of all felony cases, and the jury rules “not guilty by reason of insanity” in about 25% of these cases (2, 3). Recent studies have also shown that agreement between clinicians is high (about 79%) and that only a small minority of cases are argued in a full trial (3, 4). As in all instances of plaintiff versus defendant and state versus defendant, the judge and jury are entitled to evaluate conflicting views of expert witnesses.

Koshland’s characterization of the role of expert testimony is prejudicial. Self-styled experts blandly testifying is neither the norm for nor is limited to the insanity defense. Issues that go to trial in all areas of medicine and science will necessarily and desirably have expert opinion presented by both sides for the jury’s consideration. When all experts agree, trial is usually avoided.

Koshland is off the mark when he discusses “lumping” in mental illness diagnosis. Mental illnesses are officially and routinely categorized in more than 200 classes. Crucial distinctions among schizophrenia, manic-depressive illness, obsessive-compulsive disease, phobias, and Alzheimer's disease, for example, are routinely and reliably implemented with validating differences in treatment, course, age of onset, risk factors, neuroanatomy, and pathophysiology.

Koshland’s assertion that a biochemical measure will resolve the main aspects of a complex problem of society, law, and psychiatry is not justified by the arguments he presents, nor is it subscribed to by leading scientists concerned with mental illness. It is unwise to suggest to the public that complex criminal behavior will be adequately resolved at the level of a biochemical test.

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REFERENCES

In his editorial “Elephants, monstrosities, and the law,” Koshland addresses two related but quite different issues. Certainly there are limitations in the current ability to predict violence and problems in courtroom behavior of experts.” It is an enormous leap, however, to link legal questions of insanity with the medical diagnosis of specific mental disorders.

Forensic questions of insanity and legal culpability are entirely separate from questions of psychiatric or other medical diagnoses. Moreover, it is an illusion that greater specificity of classes of mental disorders will enable accurate prediction of future violent acts by individuals, much less distinguish violence against self from violence against others.

The assumption that mental disorders are routinely “lumped” is also faulty. While we are certainly not at the point of etiologic specificity we ultimately hope for, we have made a significant effort in the development of the third and fourth editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III and DSM-IV) to improve the reliability of psychiatric diagnosis and to establish an empirically based strat-
The weight of the world

Although the view that the brain is a biochemical organ is not in question, unlike other organs, the principal function of the brain is not to process chemicals; instead, it processes information by using chemicals and neuronal circuits. Thus, the brain seems to be much more like a computer than an organ such as the kidney. When we humans speak about the "nature of evil," our ideas would seem to arise, at least in part, from the processing of incoming information by using brain programs that were previously installed. The idea that all mental illness can be viewed simply in biochemical terms seems to rule out the possibility that an understanding of at least a subset of these diseases may also require state-of-the-art research in the sciences that study brain programming and information processing, like psychology and sociology.

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Response: My editorial was not a criticism of all psychiatrists, only of those who go beyond the data and indicate a certainty where scientific data indicate uncertainty. Bacteriologists would be incorrect to lump together all "infectious diseases" as equally curable or diagnosable, just as psychiatrists would be incorrect to lump together all mental illness as "insanity." Bacteriologists know that certain diseases can be cured by drugs and others cannot. Psychiatrists who want to testify reliably should compile data on predictable patterns of behavior and show that the predictions are verified for some defined diseases but cannot explain others. Then judges, juries, and the general public would have confidence in their opinions. Calling an ill person an "obsessive-compulsive" is of little value in a courtroom unless the diagnosis leads to accurate predictions of future behavior.

I did not state that "a biochemical measure will resolve the main aspects of a complex problem of society, law, and psychiatry." I said that some problems of mental illness are caused by malfunctioning biochemistry and that these probably cannot be helped by counseling alone.

How often the insanity defense is raised is not the issue. We still need to get at the root causes of mental illness so we can say "that abnormal behavior is caused by a deficiency of neurotransmitter z and this pill will supply it" or "that type of mental illness is not explainable yet so we can't testify either way in a trial."

Marques's argument that the brain is "programmable" makes little sense to me. The brain is designed to think, the lungs to breathe, the liver to synthesize constituents, and so forth. All depend on biochemical pathways that must function correctly for health. Bad biochemistry affects both the hardware and the "programmable" pathways, which are present in both brain and liver. Insults from the environment—bad thoughts to the brain, bad liquor to the liver—can affect these organs and so can inherited genetic defects.

I appealed for more research because both psychiatrists and biochemists have much to offer in this extremely important area, and I argue with my distinguished readers only to help identify the boundaries of knowledge for each discipline.

—Daniel E. Koshland, Jr.
she followed up 63 of those subjects (4) and, despite finding a significant relationship between contemporary blood lead and IQ, concluded, "If there are, in fact behavioral and intellectual sequelae at low levels of lead . . . these effects are minimal."

Within a year Ernhart was a grantee of the lead industry. EPA’s comments (5) are noteworthy.

[An association between lead and lower Verbal Index scores was nevertheless observed across several of the analyses (at p values ranging from 0.04 to 0.10) and . . . an association between preschool lead levels and General Cognitive Index scores approached significance at P < .09.

At a recent international meeting, T. Greene and Ernhart reported that children with elevated dentine lead levels had lower verbal IQ scores, after covariate adjustment (5). They appear to have replicated the study we published 13 years ago. Their bibliography contained no reference to the work of my group.

Scarr and Ernhart make no substantive claims against the three published meta-analyses of the field (6), all of which show a strong lead-IQ association, but they appear to dismiss two because I was the senior author. Meta-analysis is relatively free of experimenter bias if the methods are applied properly and the arithmetic is correct.

Science provides a way to transmute this debate from polemic to inquiry: Scarr and Ernhart can check my arithmetic, and then meta-analyze the same data set, including the papers published after my analyses. Others can then evaluate their conclusions—after checking their arithmetic.

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Tracing Disease Down On the Farm

Alarmed by reports of unusually high cancer incidence among farmers, the government is about to pay for a major new epidemiological study on farm chemicals and health. Three agencies—the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences, and the Environmental Protection Agency—are ready to launch an ambitious program that will monitor the lifestyles and work habits of some 100,000 farmers and their families for the next 5 years.

Although farmers tend to be longer-lived and healthier than other people, says NCI epidemiologist Aaron Blair, they have higher than normal rates of several cancers such as leukemia, melanoma, brain cancer, Hodgkin’s disease, and multiple myeloma—a cancer of the immune system’s B cells. In the study, expected to cost about $13 million, epidemiologists will look for links between these cancers and a variety of occupational hazards, including farmers’ exposure to pesticides, fertilizers, ultraviolet light, dusts, and viruses that can spread from livestock to people.

So far, this profusion of potential carcinogens has impeded efforts to link cancer to particular hazards, says Blair. The new study, however, should allow researchers to measure any difference in tumor rates between “safe” farmers and those who put themselves at risk by engaging in specific work practices.

A farmer practices “safe” fertilizer spreading.

European Observatory to Get New Chief

The European Southern Observatory (ESO) in Garching, Germany, will soon experience a shakeup in its top management. This June, ESO’s governing council is expected to name a successor to Dutch astronomer Harry van der Laan as the head of Europe’s most influential optical astronomy collaboration.

Technically, the council is not firing van der Laan—just declining to renew his 5-year contract, which runs out at the end of the year. But his predecessor held the job for 12 years before stepping down.

Described as a “forthright character” by fellow astronomers, van der Laan has reportedly annoyed ESO council members by not consulting them closely over his plans for the Very Large Telescope (VLT), a $200 million, 4 telescope array slated to open in Chile at the end of the decade. His decision to award some of the lucrative VLT design contracts to industrial, rather than academic groups, has been particularly unpopular.

Whoever takes over at ESO faces a difficult job juggling the eight-nation organization’s resources. ESO is a small outfit, with only 150 staff members. Since work on VLT began, some ESO astronomers have become dissatisfied with the pressure to work full time on the VLT, which has left them little time to pursue their own scientific interests.

Higher Temperatures For Superconductors?

Signs are beginning to emerge that the race for yet higher “critical” temperatures in high-temperature superconductors—stalled since 1988—could be heating up again. The latest competition comes from Japan, where researchers claim to have found a compound that remains superconducting at a world-record temperature of 180 degrees Kelvin.

For years, the highest temperature superconductor has been a thallium-strontium-calcium-copper-oxide compound with a critical temperature of 125 K. But at a meeting of the Japanese Society of Applied Physics in Chiba last month, materials researcher Tomoji Kawai and collaborators at Osaka University reported a major advance. They measured signs of superconductivity in three of five thin film samples of strontium-calcium-copper-oxide at the record-high temperature of 180 K—a full 55 degrees higher than the present record holder.

But caveat emptor—this well-hyped field is no stranger to dramatic claims gone bad, such as a 1990 report by Hitachi researchers of a 130 K vanadium oxide superconductor. Still, IBM physicist Zack Schlesinger says Kawai’s track record in superconductivity research gives observers reason to hope for the best. “I give it better than a 50-50 chance of being real,” he says. More details should emerge later this month in San Francisco when Kawai presents his work at a meeting of the Materials Research Society.

From left: Roybal, Mrazek, Weber, and Pursell

to a spokesman. Add to their number the members who are facing a tough reelection fight—in particular, Joseph Early (D-MA), who also bounced a number of checks—and you’ve got the formula for a major sweep.

As currently constituted, the subcommittee has dealt very favorably with biomedical research, frequently voting for NIH appropriations higher than the president’s budget request. Certainly the lobbyists who push for research funding are unnerved: “We don’t know what’s going to happen next year,” says one.
AAAS Prize for Behavioral Science Research

Entries are invited for this prize which is awarded for a meritorious published paper in the behavioral sciences. The purpose of the prize is to encourage the development and application of methods for the study of social behavior, using the logic of observation and explication so fruitful in any scientific endeavor. Entries should deal with basic observation and construction in the area known as social process, group behavior, or interpersonal behavior.

A prize of $2,500 plus a commemorative plaque will be awarded at the AAAS Annual Meeting in Boston, Massachusetts, February 1993.

Papers must have appeared in a peer-reviewed journal since January 1, 1991. Deadline for submission is July 1, 1992.

For complete guidelines, contact: Janice Merz, AAAS Behavioral Science Research Prize, American Association for the Advancement of Science, 1333 H Street, NW, Washington, DC 20005, 202/326-6621.

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ADVANCED COURSE ON GLIA AND NEURON–GLIA INTERACTIONS

Praglia Abbey, Bresseo di Teolo, Padua, Italy
October 4–16, 1992

The fourth course of the International School of Neuroscience will be on “Glia and Neuron–Glia Interactions.” The course will be open to neuroscientists enrolled in postdoctoral basic or clinical training programs. Psychiatry and neurology residents are also welcome.

The roster of lecturers will include: A. Bignami (Boston, MA, USA), D.R. Colman (New York, NY, USA), E. Costa (Washington, DC, USA), M. Dubois-Dalcq (Bethesda, MD, USA), V. Gallo (Bethesda, MD, USA), D. Giulian (Houston, TX, USA), M. Grumet (New York, NY, USA), M.E. Hatten (New York, NY, USA), K.R. Jessen (London, UK), B. Kaplan (Pittsburgh, PA, USA), H.O. Kettenmann (Heidelberg, Germany), H.K. Kimelberg (Albany, NY, USA), G. Labourette (Strasbourg, France), G. Levi (Rome, Italy), S. Murphy (Iowa City, IA, USA), R. Orkland (San Juan, Puerto Rico), B. Ransom (New Haven, CT, USA), M. Schachner (Zurich, Switzerland), B. Wise (Washington, DC, USA), J.Z. Young (Oxford, UK).

Enrollment is limited to 50 students who will be selected on the basis of their scientific merit and will represent all countries from which applications will be received.


Additional information about applications and travel grants can be obtained from Laura Linzi, International School of Neuroscience, Via Ponte della Fabbrica, 3/A - 35031 Abano Terme (Padova) Italy; Fax 049/810653-810340.
New Preparative 2-D Electrophoresis System

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Turning a Keen Eye on the Stars

By collecting starlight with widely spaced mirrors, astronomers are mapping the heavens with superlative precision. Soon they'll be turning those maps into images

On December 13, 1920, atop Mount Wilson in Southern California, the physicist Albert A. Michelson and his colleague F.G. Pease achieved an astronomical first by directly measuring the diameter of a star, the red supergiant Betelgeuse. By a technique called astronomical interferometry, they had briefly turned Mount Wilson's 100-inch telescope, then the world's largest, into the equivalent of a still-larger instrument. But the procedure—gathering starlight with two widely separated mirrors and precisely meshing its waves at the focus of the giant telescope—proved so painstaking that after a few more feats of measurement, they wrapped their apparatus in canvas and stored it away in the rafters of the telescope dome. Astronomical interferometry slipped into obscurity for decades.

Now interferometry is back in the tool kit of optical astronomers. The first of a new generation of interferometers are already racking up new diameter measurements of stars and stellar dust shells. They have teased apart close binary stars and determined key steps in the ladder of cosmic distances. And this summer, on Anderson Mesa in northern Arizona, the Naval Research Laboratory (NRL) and the U.S. Naval Observatory (USNO) will join forces to build the Big Optical Array (BOA), the first optical interferometer to turn these precision measurements into images—images of such high resolution that they could map surface features on other stars.

Michelson's technique first reemerged during the 1950s in a quite different venue, radio astronomy. But in the past 10 years, advances in sensors and control systems, together with a better understanding of the atmospheric turbulence that distorts light waves, have enabled optical astronomers to reclaim the technique. They are convinced, as BOA project manager Kurt Weiler of the NRL says, that "Michelson had the right idea—he was just 70 years too early."

Even the BOA will work on the same principles as Michelson and Pease's original interferometer, whose two collector mirrors were mounted at either end of a 20-foot girdersuspended across the opening of the telescope. Other mirrors at the center of the girders directed starlight from the outboard mirrors into the telescope, where it was combined at the focus. By gathering light with mirrors 20 feet apart, the interferometer in effect gave the Mount Wilson 100-inch telescope the same ability to resolve fine details as a 240-inch instrument.

**Delicate fringes.** The secret of an interferometer's resolving power lies in the interference pattern created when light waves from the same point in the sky are collected by the separate mirrors and then recombined. The pattern consists of alternate bright and dark bands, or "fringes"—the bright fringes appearing where the waves in the separate beams are in step and reinforce each other, and the dark ones where the waves are out of sync and cancel each other out. The interference pattern yields information about the position or diameter of a star. In diameter measurements, for example, the collector mirrors are gradually moved apart, which decreases the contrast between the dark and light bands. When the fringes vanish, the instrument at last "sees" the star as a disk rather than a point. A geometric relation between the wavelength of the starlight and the separation of the mirrors then gives the star's angular diameter.

But the pattern can be vexingly hard to interpret, because it won't hold still. Turbulence in the atmosphere can distort the wavefronts of starlight, changing the relative timing of their arrival at the different mirrors. The tiniest wobble in the instrument itself can have the same effect, by altering the length of the paths the waves have to travel from mirrors to beam combiner. Because the position of each fringe is sensitive to the slightest change in the timing of the combined waves, the result of all this unsteadiness is that the fringes jiggle wildly and drift away. "It's like trying to read the newspaper through a bubbling aquarium while jumping on a waterbed," says Weiler.

That unsteadiness defeated Pease when he tried to expand the original Mount Wilson interferometer into a 50-foot version. And it defeated would-be imitators for decades while radio astronomers, who had the advantage of working with waves 100,000 times longer than visible light, made the most of it by linking their telescopes in interferometers spanning miles—like the Very Large Array in New Mexico—or even entire hemispheres—as in very long baseline interferometers. To catch up, optical interferometry needed a way to tame the jiggles. A key breakthrough came in 1975, from a physics graduate student at the Massachusetts Institute of Technology named Michael Shao. Shao, now at the Jet Propulsion Laboratory (JPL), developed a means of introducing variable time delays into the beams. Shao's strategy is to send each beam through a "mechanical delay line": a set of moveable mirrors mounted on rails, controlled by a system that monitors the brightest fringe in the interference pattern. As the fringe shifts due to turbulence and telescope wobble, the controller moves the delay-line mirrors by as little as a few tenths of a micron every hundredth of a second. The adjustments, by changing the distance the beam has to travel on its way to the combiner, delay it by just the right amount to cancel out the jiggles. The delay line also compensates for Earth's rotation, which would otherwise cause the fringes to drift, by moving the mir-
technical secrecy is not the issue. The chemical formula and the recipes for the manufacture of LSD are in the public domain, as are the scientific facts and most of the engineering principles underlying the manufacture of nuclear weapons. In both cases, what we need to do is not to keep the technical processes secret but to make them boring. We need to make it clear to everybody that the manufacture of LSD and nuclear weapons is now a routine commercial business, no longer offering a serious intellectual challenge to bright young people. Books that present either LSD or nuclear bombs as a romantic adventure can be a danger to public health and safety.

We are here confronting an ethical dilemma that is at least 350 years old, the same dilemma that John Milton confronted in his historic battle for the freedom of the press in 17th-century England. Milton in his famous appeal with the title "Areopagitica," addressed to the English parliament in 1644, conceded to his enemies the point that books "are as lively and as vigorously productive as those fabulous dragon's teeth, and being sown up and down, may chance to spring up armed men." He conceded that the risks of letting books go free into the world could be lethal as well as irreversible. He argued that the risks must still be accepted, because the censorship of books was the greater evil. He lost the argument, and in his day the censors prevailed. In our day, the censors have lost their grip, but the ethical dilemma remains. Books have not lost their power to spring up armed men, to seduce and to destroy. The fact that this primer was declassified 26 years ago does not mean that we can spread it over the world without some responsibility for the consequences.

Perhaps I am making a mountain out of a molehill. If Serber should ever read this review he would probably say, "Shucks. It's not such a big deal." And perhaps he would be right. I hope so. With luck, this charming little book will be read only by elderly physicists and historians, people who can appreciate its elegance without being seduced by its magic.

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Macfarlane Burnet


This is a biography of one of the 20th century's great biologists, whose influence was felt far beyond the bounds of his chosen fields of endeavor, virology and immunology. It is an authorized biography, but unlike many of its genre it does not attempt to idolize or to deify its subject; the warts and blemishes are presented fairly. Indeed, Macfarlane Burnet's scientific accomplishments need no hyperbole. Trained in medicine in 1920s Australia, Burnet, innately shy and lacking in social graces, shrank from contact with patients and sought the isolation of the research laboratory. He early decided that he would accomplish great things, and hard work and a genius for generalization beyond the narrow bounds of the immediate problem vindicated this view. If Burnet had stopped with his work in virology and especially with influenza virus, he would have earned a place in the pantheon of biomedical scientists. His work on the genetic recombination of influenza virus and on bacteriophage in lysogeny helped to start the molecular biological revolution. For this work Burnet, still in his 40s, was knighted and received the Order of Merit and, among other awards, the Royal Medal of the Royal Society and the Lasker award.

Interest in the practical applications of his research led Burnet to an interest in the immune response to viral infections, and the Darwinian biologist quickly became unhappy with the Lamarckian immunochemo-