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T. Aso, W. S. Lane, J. W. Conaway, R. C. Conaway

Binding of the von Hippel-Lindau Tumor Suppressor Protein to Elongin B and C

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**Wired or Wary?**

The AAAS Board of Directors has given their new Editor-in-Chief the responsibility for planning long-term strategy for Science. Implicit in that assignment is the need to determine how best to serve our growing worldwide readership. For the past 4 years, Science, with full AAAS support, has substantially expanded its international presence by acquiring overseas editors, reporters, and members of the Board of Reviewing Editors. In addition, the editorial staff concluded some months ago that only by embracing new electronic technologies could we truly serve our international readership. Our first steps in digital communication have been intended to enhance the print publication. Although some readers retain a healthy skepticism toward Web-wired hype, this week marks a dozen issues of Science that have had electronic counterparts. Now is a great time to look back, and ahead.

Science and AAAS began offering World Wide Web (WWW) pages with the issue of 23 June 1995 at the URL (uniform resource locator) http://www.aaas.org. That issue was devoted to thorny issues of international conduct in science. To go beyond the printed stories of conflicting relations investigated by our reporters, and to bring to our readers the special interactive benefits provided by Internet communication, the Science WWW page led interested browsers to a forum in which a panel of five experts in scientific conduct, whose courses were featured in the printed stories, hosted extended discussions of real and hypothetical conflicts of interest, both intellectual and financial.

The hope that this forum would prove attractive to our readers and stimulate some international participation as well seems to have been realized. According to Features Editor John Benditt, who coordinated that issue, in the 2 months that the on-line conduct forums ran (23 June to 23 August), more than 2500 individuals participated and made more than 50,000 "hits" (or visits) to various parts of the discussion materials. Those electronic visitors came from nearly 30 different countries, including Brazil, China, Hungary, Finland, Malaysia, and Poland, and from every major sector of the Internet—universities, nonprofit organizations, government, and the commercial sector. Lively on-line discussions took place, at times involving more than 70 people in ongoing dialogues. The discussions were so intriguing that Science may reprint the entire project separately.

With that week's issue, Science also began to offer Web-browsing readers electronic versions of the "This Week in Science" page, the full Table of Contents, the Editorial, and the job recruitment advertising. "Information for Contributors" appeared in both English and Kanji (for our Japanese readers). "The People Behind Science" told prospective authors how to contact specific editors, giving information about their scientific backgrounds. The inference that these digital features meet some readers' needs is confirmed by the steady growth in the number of visitors to those pages over well 100,000 hits each week. The "Beyond the Printed Page" section has featured material that would have been impossible to provide in the printed version (such as the complete genome maps of Haemophilus influenzae from the 28 July issue). This week's special section on computers and fluid dynamics has now joined our on-line features. Once again, the Web version adds value to the printed page: links to other sites that give details on computer science research and tours of fluid dynamics simulations. The weeks to come will bring more such supplemental items.

Where do we go from here? Science probably will not limit itself to WWW communication—a gopher site has been available for some time as a means for authors, editors, and advertisers to communicate. Perhaps we will emulate offers made by some of our competitors to provide compendia of several years' worth of issues in a searchable format on CD-ROM. Science takes the view that in this rapidly moving world of scientific discovery and application, the critical need is not simply for more rapid communication, but for a way to transform floods of data into perspectives that scholars can incorporate into their own evolving views of those elements of the scientific enterprise they choose to follow or sample. Our goal will be to facilitate the dialogue among scientists interested in common topics, methods, or applications, much as we did in our inaugural discussions of scientific conduct. How exactly will we offer these and other electronic reader services? Stay tuned.

Floyd E. Bloom
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The Discipline of Epidemiology

In the Special News Report “Epidemiology faces its limits” (14 July, p. 164), Gary Taubes assembles a series of quotations from ourselves and others about potential methodologic pitfalls in epidemiologic studies that might leave readers with the misimpression that evidence based on epidemiologic findings is not usually credible.

A problem does exist with general media reports about single scientific studies. Such reports often herald new results without describing the scientific context, which can create unnecessary fear and confusion. However, this is more an abuse of epidemiologic evidence than a problem with epidemiologic research. Taubes seems to perpetuate this confusion by listing several media reports of published findings and telling the reader “you be the judge” (p. 156) when proper judging is impossible without substantial additional information. In any scientific field, findings of individual studies are usually not considered seriously until confirmed by others. Also, in epidemiology, as in any other scientific field, more powerful studies need to be conducted to evaluate smaller effects, where sources of bias may be especially problematic. Often, doing so will require large and long-term prospective studies with repeated measures of exposure based on both questionnaires and biological measurements; a substantial number of such studies have commenced over the last 15 years.

Taubes did not emphasize that what we do know about the prevention of cancer and cardiovascular disease has derived largely from epidemiologic findings. This knowledge includes not just the many adverse effects of cigarette smoking, but also the relation of overweight to many diseases, the benefits of increased physical activity for cardiovascular disease, the effects of many occupational exposures (such as benzene and asbestos), the relation of exogenous postmenopausal estrogen to cancer of the uterus, the relation of sunlight to all forms of skin cancer, the relation of ionizing radiation to many cancers, the adverse effects of many pharmacologic agents (for example, DES and thalidomide), and the protective effects of high intake of fruits and vegetables against many cancers.

Epidemiology has also provided important reassurance that many aspects of daily life are not major risk factors. For example, the relation between coffee consumption and coronary heart disease may not be completely settled, but the danger is minimal: The uncertainty is whether as much as five cups per day is a weak risk factor or not a risk factor at all (1). Fear of saccharin carcinogenicity engendered by studies in rats was quelled by epidemiologic research. Furthermore, epidemiologic studies have provided clear evidence that the incidence of several other forms of cancer, including ovarian cancer, is lessened as a consequence of using birth control pills.

If we wish to continue our progress in understanding the importance of lifestyle and environmental risk factors, we have little choice but to monitor the occurrence of illness of persons who have and have not been exposed to such factors. As Bruce Ames, a molecular biologist at the University of California, has noted (2), advances in other biological sciences can greatly add to the power of epidemiologic studies, but cannot replace them.
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Taubes's report is insightful and useful for epidemiologists and nonepidemiologists alike. However, I have two objections, one of them of personal nature, the other more general.

Taubes writes that I have expressed the view that only a fourfold risk should be taken seriously. This is correct, but only when the finding stands in a biological vacuum or has little or no biomedical credibility. We all take seriously small relative risks when there is a credible hypothesis in the background. Nobody disputes that the prevalence of boys at birth is higher than that of girls (an excess of 3%), that men have a 30% higher rate of death compared to women of the same age, or that fatality in a car accident is higher when the car is smaller.

The more general issue is that Taubes has omitted a consideration that is of paramount importance in any scientific argument. Epidemiology should be evaluated in comparison to other disciplines that serve the same objective, that is, to identify the causes of human disease and facilitate their prevention. Among these disciplines, only epidemiology can document causation without concern about dose-extrapolation or species variability and with built-in accounting for potential modifiers.

It could be said for epidemiology, with respect to disease etiology and prevention, what is frequently said about democracy as a system of government: They both have many problems and weaknesses, but they still represent the best available approach for the achievement of their respective objectives.

Dimitrios Trichopoulos
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Taubes's excellent article about the proliferation of health-related messages to the public, and in particular the role of the popular press in their promulgation, misses one factor driving this process. Research institutions are eager to have the results of health risk factor studies performed in their laboratories appear in prominent newspapers and news magazines. This is so because individual philanthropists like almost nothing better than to support institutions whose research efforts have appeared on
The limits of epidemiology for environmental studies are well covered by Taubes. Genetic epidemiology is quite a different story. Clustering of cancer in families has led to the recognition of tumor suppressor genes by Alfred G. Knudson Jr. through study of retinoblastoma in childhood (1). These genes have since been found in other cancers of children and some of the commonest cancers of adults. Epidemiologic identification of the diverse familial cancers that cluster in Li-Fraumeni syndrome led to laboratory research that has furthered understanding the role of the p53 gene in carcinogenesis (2). New clues to the origins of neoplasia are also coming from laboratory studies based on cancer clusters in heritable disorders, such as ataxia-telangiectasia (3). Genetic epidemiology should not suffer guilt by association with the downside of its environmental counterpart.

Robert W. Miller
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References

When critics of epidemiology pay homage at the altar of the randomized clinical trial, such trials are made to sound only moderately troublesome compared to observational studies, when in fact they are often absolutely impractical or absolutely unethical. Examples include randomizing women to method of birth control and individuals to diet.

For such research, observational studies are the only recourse if you want to work with humans. The future and power of epidemiology rest not with simply self-reported data, but with combining such information with molecular data on susceptibility. In this way, risk measurements reflect characteristics of both host and environment and make targeting prevention strategies rational. The challenge will be to use these host factors, such as genetic data, in a socially acceptable and nonpunitive fashion. Then epidemiology will provide truly meaningful and relevant estimates of risk.

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Most of the epidemiology of multifactorial diseases fails a test of method, due to absent experimental randomization and unachievable control of biases and confounders. In general, it also fails the ultimate test of predictivity, as large randomized experiments designed to verify major observational inferences have been thoroughly disappointing (1). Now, a resounding admission of impotence threatens our survival and demands remedial measures.

As other professionals have done, epidemiologists could establish a code of good practice, spelling out optimal standards of hypothesis formulation, study design, and conduct. Structural uncertainties should limit heuristic causal inferences to relative risk or odds ratio values above 3 or 4, as Trichopoulos (quoted in the article by
fluctuations in the survival of juveniles of these species. Not does the article mention the likely expenditure of $350 million on habitat protection in the spill area.

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Robert B. Spies*
Applied Marine Sciences,
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*Chief Scientist, Exxon Valdez Trustee Council

Successful Grants Management

In his letter "Funding of NIH grant applications: Update" (7 July, p. 13), H. George Mandel presents new data about the funding of unsolicited, unamended, competing National Institutes of Health (NIH) research grant applications. He demonstrates effectively that the overall NIH funding rate for both new and renewal applications has fallen steadily over the last decade. This has certainly been the case at the National Eye Institute (NEI), the institute from which I receive funding and on whose council I have served. At NEI, the success rate fell from 47% in 1985 to 36% in 1994, and the total number of research project grants funded also fell significantly over that period. Mandel points out that the funding rate at NEI is higher than that of most other NIH institutes and centers, but does not comment on why this is so.

From 1985 to 1994, NEI's share of the total NIH budget dropped from 3.3% to 2.7%. Therefore, NEI did not simply outspend the other institutes and centers. Rather, NEI has used its extramural funds for basic research in such a way as to maximize opportunities for individual investigators. The vision research community has been extremely supportive of this strategy and credits it with fostering the extraordinary progress in this field. Historically, NEI has devoted proportionately more of its extramural resources to traditional research project grants than has any other disease-oriented institute at NIH. Moreover, within the research project grant category, NEI does not award program project grants or other types of "umbrella" mechanisms of research support. NEI does not fund clinical trials or other types of large applied clinical research projects using R01-type mechanisms. In addition, NEI rarely issues requests for applications or program announcements and, therefore, does not artificially drive up the number of competing applications. In summary, this series of management decisions has had the direct effect of increasing the NEI success rate of grants awarded relative to that of many of the other NIH institutes and centers.

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Corrections and Clarifications

In the caption in the left margin of the Table of Contents in the issue of 18 August (p. 898), the gene located on chromosome 1 was incorrectly described as the second candidate familial Alzheimer's disease gene to be identified. The caption should have read, "A third familial Alzheimer's gene."

In the report "Localization of targets for anti-ulcer drugs in cells of the immune system" by E. Mezey et al. (4 Dec. 1992, p. 1662), on page 1662, in the second column, on the fourth line, the word "antagonists" was incorrect. The sentence should have read "Dopamine also modulates gastric acid secretion (4), and dopamine agonists prevent ulcer relapse (5)."
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Panel A: Long read, high resolution Differential Display data provided by Drs. Lidia Averbouk and Arthur Pardee, Division of Cell Growth & Regulation, Dana-Farber Cancer Institute. Samples run on genomyxLR (2.5 hr, 100 W, 3 kV, 50°C, HR-1000 4.5% Denaturing gel). Data represent display patterns under different RT-PCR conditions using total cellular RNA from LNCaP-FGC prostate carcinoma cell line. All reactions performed with the GenHunter RNAimage™ Differential Display Kit.

Panel B: Long read, high resolution Differential Display patterns of total cellular RNA from HeLa and transformed rat fibroblast cells using GenHunter RNAimage Differential Display Kit. Samples run on genomyxLR (2.5 hr, 100 W, 2.7 kV, 50°C, HR-1000 6% Denaturing gel). Data provided by GENOMYX Corporation.

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</tr>
<tr>
<td>Microsatellites</td>
<td>2 nt resolution, 0.5% sizing precision</td>
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<td>SSCP</td>
<td>0.5% pattern matching precision</td>
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Conclusions

Many processes need to be considered in interpretations of terrestrial and planetary landforms. Until the advent of modern computers, complex internal fluid-dynamic processes such as those illustrated here could not be easily considered because the highly nonlinear processes are not susceptible to analytic or semianalytic analyses. The use of numerical simulations to solve and visualize fluid-dynamic processes and constraints can be combined with laboratory and field observations to enhance our understanding of complex geologic phenomena on Earth and on the other planets.

REFERENCES AND NOTES

24. DASH is a computer code developed at Los Alamos National Laboratory to study dusty air shocks. The simulations reported here took several to dozens of hours on an SGI Indigo II workstation.
32. Supported by NASA grants NAGW-1740 (at Arizona State University) and 5-56791 (at the University of British Columbia). Related preliminary work on DASH was supported by Los Alamos National Laboratory Institute of Geophysics and Planetary Physics. I was greatly assisted in various stages of this project by A. Levine, T. Morino, M. Morrissey, M.-L. Woo, and G. Yuan. Special thanks are due to G. Valentine and K. Wohletz for continued wisdom on DASH.

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should be an answer to the Soviet test. Most agreed that the nuclear production capability of the AEC should be increased. But some felt that more was needed.

Ernest Lawrence, the inventor of the cyclotron, and Luis Alvarez, who was doing ingenious experiments using it, decided the time had come to make a major effort to develop Teller’s thermonuclear weapon, the Super. They went to Washington and found enthusiastic support from the JCAE. The AEC was divided and asked the GAC for advice. At a meeting of the GAC at the end of October 1949, Oppenheimer asked all members to express their opinion before he gave his own. There was unanimous opposition to a crash program to develop the Super.

The military usefulness of the Super was questioned. Assuming that both sides would get the Super, the security of the United States would be further diminished if the yield of the bomb were increased by another factor 1000. The members of the GAC also felt it was morally wrong to introduce this additional step into the arms race.

The GAC did not prevail. After heated debate in Washington, President Truman decided in January 1950 to go full steam ahead with the thermonuclear development.

The trouble was that there was no design available. Teller’s “classical Super” turned out, in many calculations by Ulam and others, to be far more difficult and costly than expected. There was the alternative of the Alarm Clock, but its yield was strictly limited. The lure of unlimited yield of the classical Super was irresistible.

So it went for a year, until early in 1951, when Ulam had the idea of compressing a thermonuclear secondary with the hydrodynamic shock produced by a primary fission bomb. Teller accepted the idea, improving it by using the pressure of the radiation from the primary, rather than hydrodynamic shock. The idea was immediately persuasive to everybody, including Oppenheimer, the GAC, and the AEC. Los Alamos, in 17 months, produced the first thermonuclear device, proved in the Mike test in the Pacific and yielding over 10 megatons.

This and many other developments are described in fascinating detail in Dark Sun. I can only admire the thorough research that is the basis of this book. Most of the story of the spies was new to me, and even some of the difficult engineering leading to the successful test of Mike. There were many conflicts of personality, in Washington and in Los Alamos. The book is full of suspense. Its only fault is that it kept me from doing other work.

Hans A. Bethe
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The Enola Gay Script


The controversy that led to the cancellation of the Smithsonian Institution’s Air and Space Museum exhibit centered on the Enola Gay, the airplane that dropped the atomic bomb on Hiroshima, has attracted much attention both here and in Japan as the 50th anniversary of the event has loomed on the horizon. Those who have pondered at second hand the expressions of outrage the planned exhibit evoked from veteran’s groups and others and the generally quieter voices charging distortions in the critics’ representations of the content of the exhibit will in this book find an opportunity to make some assessment of the matter for themselves. The book reprints, verbatim according to the editor, the original script for the exhibit, entitled “The Crossroads: The End of World War II, The Atomic Bomb, and the Origins of the Cold War.” Beginning with a recommendation that “parental discretion is advised” and concluding that the “dilemma” posed by nuclear weapons “is not about to disappear,” the 127-page script is divided into five main “units” with numerous subunits, typically about 200 words in length. The photographs and captions that were to be included in the exhibit are not included, but the script contains a small amount of other illustrative material. Only about a third of the book is given over to the script itself, which is placed between two essays by commentators obviously sympathetic to the original conception of the exhibit. In a 90-page introduction Nobile recounts and comments on the controversy in a punchy style, for instance characterizing Air Force historian Richard Hallion, whose 1993 memo characterizing the text as “a great script . . . obviously based on a great deal of sound research” is quoted on the cover of the book, as “prematurely honest. Faster than you can say Pearl Harbor, he got with the Pentagon program and morphed into an ardent enemy of the Smithsonian.” A still lengthier afterward by Stanford University historian Barton Bernstein, who was a member of the exhibit’s Advisory Board, summarizes the various views concerning the decision to drop the atomic bomb that were expressed by political and military leaders of the time or have been developed by scholars since the event and gives his own commentary on the Smithsonian events, expressing the hope that though in the short run the opponents of the exhibit defeated the Air and Space Museum’s attempt at “distilling the existing scholarship on the A-bomb for public consumption” the controversy itself will bring heightened attention to the issues. Both Nobile and Bernstein (the latter with over 200 notes) cite a variety of source material bearing on the controversy, and the book includes an index to the exhibit script. A note from the publisher states that the work was prepared without any participation from Smithsonian staff.

Katherine Livingston

Books Received


Publishers’ Addresses

Below is information about how to direct orders for books reviewed in this issue. A full list of addresses of publishers represented in Science appears in the issue of 26 May 1995, page 1220.


**PRODUCTS & MATERIALS**

**DNA Quantitation Kit**
The Beacon DNA Quantitation Kit contains a fluorescent dye that selectively binds to double-stranded DNA, producing an amplification of fluorescence intensity of the dye. The method allows specific quantitation of double-stranded DNA, with minimal detection of single-stranded nucleic acids. The procedure involves generating a standard curve by serially diluting a DNA standard. A best-fit line is then constructed by linear regression and used to determine the DNA concentration of unknown samples. The kit can be used to generate both high (3 to 200 ng) and low (0.098 to 25 ng) DNA standard curves. *PanVera. Circle 139.*

**Antibodies**
Antibodies for the study of proteins involved in cell adhesion include antibodies to the catenins (α, β, and γ), E-cadherin, P-cadherin, cadherin-5, cadherin-11, desmoglein, and L1 glycoprotein. The antibodies can be used in protein immunoblotting and immunocytochemistry. *Transduction Laboratories. Circle 140.*

A full line of purified polyclonal cytokine antibodies includes antibodies against IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-13, IL-15, EGF, FGF-β, GM-CSF, IGF-I, IGF-II, IFN-α, IFN-γ, MCAF, MIP-1α, RANTES, TGF-α, TNF-α, TNF-β, and VEGF. Murine polyclonal cytokine antibodies are available for IL-1α, IL-1β, IL-3, IL-4, IL-6, GM-CSF, and TNF-α. *CytImmune Sciences. Circle 141.*

**DNA Sequencer**
The ABI PRISM 377 DNA Sequencer produces genetic information four times faster than previous technology for sequencing, linkage, and mapping projects, according to the manufacturer. The new sequencer can collect data at rates of up to 7200 bases per hour, compared with 1800 bases per hour for its predecessor. The sequencer’s new user interface streamlines data collection and analysis with fast, efficient gel pouring and handling. The new instrument requires thinner gels and less sample. It accommodates 12-, 36-, and 4-cm well-to-read lengths. By adjusting speed in combination with gel length and resolution, users can optimize performance to match their DNA sequencing and fragment analysis requirements precisely. *Perkin-Elmer. Circle 142.*

**Pharmacokinetic Data Analysis Software**
PKAnalyst is a Windows update of the RSTRIP pharmacokinetic software program. New features include hypertext-based online help, three-dimensional line and surface plotting, more intuitive graphics interaction, and a more powerful text editor. It has more than 2 dozen pharmacokinetic models built in. It can calculate micro-rate constants for compartmental models, analyze saturable kinetics, handle bolus and zero- or first-order input for finite and infinite time periods, simulate pharmacokinetics with multiple dosing, or with both bolus and infusion occurring together, and produce concentration/effect Sigmoid-Emax diagrams. *MicroMath Scientific Software. Circle 143.*

**DNA Elution from Agarose Gels**
Two new methods for elution of DNA from agarose gel blocks using Ultrafree-MC centrifugal filters are the 5-min method and the...