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Figure Legend: Autoradiograph of sequencing gel using the BaseAce Sequencer and the FeatherVolt 2000 power supply. 1.0 μg M13 ssDNA was labeled with S-35 ATP and run for 3 hrs at 65 watts on a 6% acrylamide (7M Urea, 1X TBE) gel.

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Spiral calcium wavefronts in a Xenopus laevis oocyte expressing muscarinic acetylcholine receptors observed by confocal microscopy. This spatiotemporal pattern of calcium activity (normal projection of five images collected over 10 seconds) is characteristic of a regenerative excitable medium and suggests that the calcium-mobilizing machinery behaves as such. See page 123. [Image by J. Leichleiter and co-workers]
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Industrial Interactions with Universities

Many university administrators seem to believe that research conducted by staff can be exploited through patents and innovations to produce substantial revenues for their institutions. A recent publication of the National Academy Press provides a contrasting view of the industrial interactions with universities. The report is a summary of interviews with 17 senior industrial officials.*

Bringing profitable products to market requires a different set of motivations, organization, and culture than does the creation and dissemination of knowledge. Companies have also noted that for every $1 spent on research $10 is devoted to development and $100 to design and construction of plants. Much of this activity requires participation of goal-oriented interdisciplinary teams.

In many industries a major activity is to improve quality or manufacturing processes of existing products. This often occurs through small incremental improvements. The report notes that “incremental technological advance . . . is the dominant step in the process of innovation . . . related to competitiveness and international trade.” Parenthetically, most of us are aware that an important factor in Japanese economic triumphs has been their vigor in improving existing products for which there was already a market.

Most of the industry officials interviewed supported the view that “industry is the primary source of innovation because industry fosters entrepreneurial awareness of profitable emerging fields and ideas . . . [and that] industry scientists and engineers know more about a technology, its detail, and its system than do academic scientists and engineers. Industrial scientists . . . tend to be better at setting goals and at interdisciplinary research and can assess what needs to be done to develop a field.” An exception is in biotechnology where advances require close collaboration with research at universities. In general, how much companies rely on universities varies with the technical field, the maturity of the industry, the stage of research, and the size of the company.

All the officials interviewed mentioned the importance of collaboration with universities, which furnish new knowledge needed to build new technologies and to improve old ones. But companies can be discriminating in the choice of fields in which to collaborate. Some of their most valued assets are their stores of proprietary information, guarded zealously. Martin Marietta prefers to fund research at universities that will provide entry into an area where the firm has only limited expertise. “Otherwise,” said Albert R. C. Westwood, “the flow of information tends to be from the company to the university.”

Considerable attention in the report is devoted to the various forms that collaboration takes. These include participation in consortia, centers, affiliates, large multimillion-dollar university–single company alliances, and one-on-one interactions of university and industry scientists. It is the latter form of collaboration that is now most favored. It may involve support by a company for an individual’s research that is being conducted at a university, or it may take the form of consultation by professors at industrial research facilities. The industry officials interviewed were cool toward other types of arrangements.

Consortiums and centers that include participation of several companies may be effective in basic science and in addressing generic issues in the development of new technologies, but they are said to be unlikely to have a significant role in the process of innovation. Companies are less and less interested in participating in industrial affiliates’ programs or in consortiums. S. Allen Heiningier of Monsanto, who is president of the American Chemical Society, commented on Monsanto’s large multimillion-dollar alliances with Harvard and with Washington University. He took the position that these two major collaborations have not yet demonstrated success. He said that products need to be developed if a major collaboration is to be judged successful for both parties. Otherwise, “Monsanto’s participation becomes a charitable donation to the university.”

In many ways the report outlines the magnitude of the chasm that exists between the viewpoints and culture of universities and industry. Heiningier attributes part of the chasm to the mechanisms of federal funding of university research. Peer-review decisions have emphasized the pursuit of scientific knowledge while not necessarily providing a balancing input of what society’s future needs are likely to be. —PHILIP H. ABELSON

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Goldstein and Kalant recognize the hypocrisy of the present differential prohibitions of psychoactive compounds. The authors are brave to call for decriminalizing the possession of small amounts of drugs, needle exchange programs, and treatments that begin by making the individual's drug of choice available. Unfortunately, the intensity of the "war on drugs" makes it difficult for even these authors to fairly estimate the hazards of revising the regulations for psychoactive compounds.

Goldstein and Kalant argue against drug legalization, fearing that the removal of explicit legal sanctions and subsequent increases in availability will lead to increased drug abuse. Data that are admittedly weakened by "the absence of sound national surveys" are cited to support the assertion that legalization would lead to an "increase in use [that] would be very large." However, the careful reader will find buried in reference 58 a more stringent evaluation; Goldstein and Kalant discredit similarly anecdotal reports that reducing penalties for possession of marijuana did not lead to substantially increased use of the drug in Holland or in many U.S. states. The authors note that "drug use has been declining ... for all psychoactive drugs whether licit or illicit." Does not reduced consumption of cheap and legal drugs such as caffeine and nicotine imply that a well-educated, free citizenry can make healthful decisions about drugs in the absence of punitive legal sanctions?

Goldstein and Kalant lament that a rational drug policy may be impractical since scientific evidence does not compete well with "long-established values and practices." The authors themselves prove this point, as their proposed changes in drug policy perpetuate a bias in favor of legal drugs and in opposition to illegal drugs. Implementing their suggestions would leave a vast discrepancy between the relative legal status and relative harm of drugs such as marijuana and alcohol. A society that holds freedom to be a basic value should be able to implement a drug policy based on science and should be able to develop means of discouraging drug abuse without recourse to hypocritical prohibitions.

Response: Hollister is quite right in emphasizing the relatively much greater damage to health from licit substances, including prescription drugs, than from illicit ones. We agree completely, and did point this out in several places in our article. Moreover, we also cited the triple prescription program as a measure that had proven effective in reducing the abuse of benzodiazepines. We differ from Hollister only in the relative emphasis placed on different types of licit substance. Hollister cites statistics demonstrating that prescription drugs account for the great preponderance of emergency room visits and acute drug-related deaths. We have put more emphasis on the much greater total damage, including chronic illness and death, attributable to abuse of other licit substances, specifically alcohol and tobacco. The point on which we obviously agree is that it is essential to retain proper perspective in viewing the problems of drug abuse and to recognize that these are most definitely not confined to illicits "street" drugs.

Lukas' criticisms are well taken, and we must plead guilty to using terms that are not satisfactorily defined operationally. We were aware of this when we wrote our article. Indeed, one of us (H.K.) was a member of the World Health Organization working group (1) that proposed the term "neuroadaptation" and that rejected the term "drug abuse" because of its lack of definition and its obvious value-judgmental character. However, we chose to use the terms "addiction" and "drug abuse" for a practical and significant reason. The article was meant to be read, as we believe it has been, by people

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from a broad range of backgrounds, many of whom are not acquainted with the specific scientific concepts to which Lukas refers. We felt it better to write in terms that a general public knows and uses, so that attention would be directed to the major social policy issues surrounding the drug-related problems, rather than to the scientific analysis of the nature of dependence itself.

This is illustrated by our relative ranking of "risk of addiction" for different classes of drugs in our table 1. Lukas is correct in surmising that our rankings reflect "a mixture of scientific, social, and economic factors." Again, this was a deliberate choice. We acknowledge the scientific validity of Lukas' terminology; indeed, one of us (H.K.) was a contributor to the manual by Brady and Lukas (2) on scientific testing of drugs for their dependence potential and abuse liability. However, virtually every investigator in this field recognizes that the prevalence of problems attributable to any particular drug reflects not only the intrinsic pharmacological reinforcing effects of the drugs themselves, but also the influence of availability, fashion, social norms and current attitudes and beliefs. Our ranking was an (admittedly somewhat arbitrary) attempt to take these all into consideration. For example, if we had used only the results of test models such as those described by Brady and Lukas (2), we would not have included the hallucinogens at all, because they have proven to be aversive rather than reinforcing in animal models. Nevertheless, a few humans who use the drugs become sufficiently devoted to them to incur harmful consequences that justify inclusion of these drugs at the lowest level in our table.

Lecese appears to be suggesting that we supported our argument about the influence of easy availability on extent of drug use by referring to data that we ourselves recognized as faulty. This is not true. We noted the absence of sound national survey data about opiate use before the passage of the Harrison Act, but pointed out that Terry's work provided at least a valuable set of data for a circumscribed jurisdiction.

If Lecese's main contention is that "a well-educated, free citizenry can make healthful decisions about drugs in the absence of punitive legal sanctions," we agree with him completely. We stated, with respect to marijuana, "If preventive education achieves its goals, and public attitudes and other nonlegal controls over cannabis use become strong enough, it might eventually be possible to loosen the regulatory controls without risk of a major increase in use and the likely attendant problems." This would indeed be the ideal goal with respect to all drug use in a well-educated, free democratic
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Leucine, L. [4,5-3H]
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society. But merely wishing it to be so does not automatically make it so. Our point is that it takes time and major effort to reach that desirable state of educated individual decision. In the interim, restrictive regulations can complement educational efforts in changing social consensus. In moving toward the ultimate goal, it is necessary to proceed cautiously and pragmatically, to avoid making things worse than they now are.

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REFERENCES

Alzheimer's Disease Cell Bank

The News briefing “Cell bank for mental illnesses” (11 Jan., p. 159) may have led some readers to mistakenly conclude that the National Institute of Mental Health's National Cell Repository is “the first nationally coordinated initiative to aid researchers in defining the genetic basis for Alzheimer's disease. ...”

In fact, the National Institute on Aging-supported Alzheimer's Disease Research Center National Cell Bank has been in operation since September 1989 at Indiana University, in collaboration with Duke University. It is devoted to providing lymphoblast cultures from patients and family members with clinically diagnosed and pathologically confirmed Alzheimer's disease to investigators nationwide in an effort to speed the determination of the genetic defect that is associated with Alzheimer's disease.

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Erratum: The seventh sentence of the first paragraph of the letter from P. W. Anderson, E. Abrahams, and R. Laughlin that appeared in the issue of 1 March (pp. 1005–1006) was printed incorrectly. It should have read, “Others, such as the ‘anyon’ proponents, a group at Bell laboratories and Rutgers, and another at Princeton, are sure that this system is not a Fermi liquid.”
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"The bad news is that he's writing a book about the treatment of animals."
We thank B. Nodes for technical assistance, W. Yang and W. Hendrickson for providing the refined 1.7 Å coordinates of E. coli RNase H, and C. Janson for helping in crystallizations. Coordinates for the model described have been submitted to the Protein Data Bank. Supported in part by NIH grant GM 39599.

7 February 1991; accepted 7 March 1991
ease. We do not advocate new ablative therapies for parkinsonism, and agree with Aebischer and Goddard that more animal research is needed on the mechanism by which parkinsonian motor signs develop. Nonetheless, possible implications of our findings for future clinical applications cannot be ignored.

The finding of Aebischer and Goddard supports the hypothesis that reducing the output of the globus pallidus (GPI) in monkeys treated with MPTP is sufficient to reduce parkinsonian signs. However, the inconsistencies they perceive between the results of lesions in primates and in humans seem more apparent than real. It is widely accepted that thalamotomy is useful against tremor and rigidity, while it is not effective against akinesia (2); but there are at least two larger, well-documented studies which indicate that pallidectomies in humans reduce all major parkinsonian signs, including akinesia (3). Regarding the effects of lesions, experimentation in animal models lags behind clinical experience with humans. We agree that such therapies of Parkinson’s disease need to be explored in animal models before clinical trials are carried out.

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REFERENCES

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Eugenics: a scholarly undertaking ever more "a chapter" on statistical inference (pp. 1–244), another substantial chapter on statistical theory and method (pp. 245–306), and a grab bag of short chapters on topics such as history, philosophy, teaching, and scientific research (pp. 307–360). The correspondence, arranged in each section alphabetically by name of correspondent, covers the full 40 years up to Fisher's death in 1962 but has only two main contributions from the 1920s and is weighted to the mid-1950s, when Fisher was preparing the short summing-up volume Statistical Methods and Scientific Inference that appeared in 1956.

Fisher's originality and genius sparked a major share of the statistical developments of the 20th century. His most productive period began in the 1910s with analytical representations of sampling distributions and continued through the 1920s with key conceptual and technical developments in estimation theory. The middle of the decade saw the publication of the first of many editions of the pathbreaking Statistical Methods for Research Workers. In parallel with these works, Fisher made major contributions to genetics, leading to the 1930 publication of The Genetical Theory of Natural Selection. The flow of innovative papers on statistical theory and methods continued through the 1930s and included the 1935 publication of Design of Experiments.

Although he was widely recognized and honored, for example by election to Royal Society fellowship in 1929, Fisher's career was marred by animosities directed at individuals who criticized him, often not understanding his radically new ideas. Frictions with Karl Pearson developed early and continued through Pearson's death despite wide acceptance of the merits of Fisher's positions. In the 1930s, Fisher increasingly interacted with the British-American school of mathematical statisticians who took his ideas as a starting point, and he became embroiled in bitter controversies, especially with theoreticians led by Jerzy Neyman, who in Fisher's eyes distorted his positions and substituted unsound and dangerous theories in place of his own. Fisher returned with vigor to statistical controversies in the 1950s but achieved quite limited success in persuading theorists to stay on his side. A few months before his death, he would refer to "that darkest Continent, N. America!" (p. 215).

I find few important revelations in Fisher's letters, but there are many pungent statements of attitudes and positions that can deepen understanding of applied statistics and the logic of statistical inference, especially if read in conjunction with the well-signposted papers and books that Fisher was writing, revising, and discussing with friendly colleagues. Along with having direct teaching value, the letters will be an enormous resource as statisticians and other scholars increasingly seek to research, review, and place in scientific context the development of 20th-century statistics. It is never too soon to start, but the dust has not entirely settled on the arguments of 35 years ago, and it is only in recent years that we have achieved balanced views of the period up to 1900 in distinguished books by Theodore Porter (The Rise of Statistical Thinking, Princeton University Press, 1986) and Stephen Stigler (The History of Statistics, Harvard University Press, 1986).

The most prominent themes throughout the letters concern the gradual evolution of Fisher's thought on probability and related concepts of what he called the logic of uncertain inference. Large fractions of the text are devoted to lengthy exchanges with H. Jeffreys (9% of the text) in the 1930s, French colleagues G. Darmois (4%) and M. Fréchet (7%) centering on 1940, and British colleagues G. A. Barnard (12%) and D. J. Finney (6%) over the final 15 years but peaking in the mid-1950s. The exchanges with N. Campbell in 1922 give a look at Fisher's early, mainly frequency-based ideas on probability. The long series with Bayesian geophysicist Jeffreys says much about both men and may be the most important part of the book, including Fisher's interpretation of Bayes's prior probability as "a value averaged over objective frequencies" (p. 167), which was not accepted, or perhaps understood, by Jeffreys, and containing illuminating discussions of Laplace's concept of "equally possible" cases and Fisher's concept of a "hypothetical infinite population." Fisher put much effort into elaborating his "fiducial argument" and distinguishing its logic from the simpler Neymanian concept of confidence limits that developed from the earliest of Fisher's writing on fiducial intervals. Technical aspects of the fiducial method were discussed in correspondence with D. A. S. Fraser, L. J. Savage, and J. W. Tukey, occupying 10 to 13 pages each in this volume, and are reflected in many of the other letters in the long chapter 1.

Fisher was broad in his outlook toward probability and came to regard fiducial probability as very much in the spirit of classical writers such as Bayes. He did not oppose Keynes's "measure of rational belief" interpretation, which he called "penetrating" and "needed" (p. 56), but he regarded it as too all-embracing and attempted to formulate a system of logical varieties appropriate to varying circumstances. The interpretation of significance tests and the explanation of concepts related to likelihood are frequently discussed in the letters.

I am slighting in this review the many illustrations of practical statistical thinking that Fisher generously provided in response to inquiries from far and wide. The correspondence shows little of the irascible nature that made Fisher's jousts with opponents in published discussions famous. He is mainly polite and occasionally shows a jocular and fun-loving side. He was barely tolerant of able young statisticians such as M. S. Bartlett, S. S. Wilks, and J. Wishart, whom he would berate, I believe unfairly, in the early 1930s, suggesting they had not read his original papers when they attempted alternative derivations and elaborations of his models. Fisher did not always attempt to follow the technical arguments that correspondents bounced off him, even when they nominally concerned his own fundamental principles, being more concerned to repeat and polish his own formulations. And for this concern subsequent generations will be grateful, for Fisher expresses deep ideas with brevity and penetration. Although they do not make easy reading, the effort of following his arguments is always repaid.

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Books Received


**Schizophrenia Research.** Carol A. Tamminga and S. Charles Schulz. Eds. Raven, New York, 1991. xvii, 373 pp., illus. $120. Advances in Neuropsychiatry and Psychopharmacology.


**The Unreal Life of Oscar Zariski.** Carol Parikh. Academic Press, San Diego, CA, 1990. xviii, 264 pp., illus. $32.95.
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