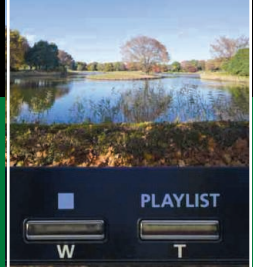
Sisters, brothers, bonds
1349



Media money for conservation?
1351

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LETTERS

edited by Jennifer Sills

Rethinking Clinical Trials: Phase 1 Studies Insufficient

IN HIS EDITORIAL "RETHINKING CLINICAL TRIALS" (23 SEPTEMBER, p. 1679), A. Grove proposes returning to the era before the enactment of the 1938 Federal Food, Drug, and Cosmetic Act, when new drugs were marketed in the United States without evidence that they were safe or effective. His irrational and dangerous proposal, which would limit the Food and Drug Administration's (FDA) premarket review of new drugs to phase 1 clinical trials, is premised on the fundamental misunderstanding that such trials can provide proof of a drug's safety and on the misguided belief that it is not necessary to establish proof of efficacy.

Phase 1 trials typically involve exposing 20 to 80 participants (who are usually healthy but sometimes diseased) to a single dose of a new drug and collecting data on short-term toxicity as well as drug metabolism and excretion. In most phase 1 trials, serial small cohorts of subjects are exposed to increasing doses of a drug in order to define the highest dose that does not result in unacceptable toxicity. Data from such studies guide dosing in subsequent phase 2 and phase 3 trials.

Phase 1 studies are not designed to prove that a drug is safe in healthy individuals, let alone diseased patients for whom the drug is being developed. Indeed, the most important evidence regarding the safety of new drugs is obtained routinely in subsequent phase 2 and 3 trials, which involve many more subjects, longer drug exposure, and much longer follow-up than phase 1 trials. Many new drugs are not approved by the FDA because phase 2 and 3 trials demonstrate that the drugs' risks outweigh their benefits, both of which are measured in these trials.

Grove's proposal would subject patients on a massive scale to haphazard, uncontrolled, poorly regulated experimentation involving drugs with unknown safety and effectiveness. Such a flawed proposal does not deserve serious consideration.

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Rethinking Clinical Trials: Change Is Coming

IN HIS EDITORIAL "RETHINKING CLINICAL trials" (23 September, p. 1679), A. Grove suggests the provocative idea of using e-commerce software and data-mining techniques to conduct clinical trials and to streamline the process of making newer drugs accessible. There is no question that the present legacy system of three-phase pharmaceutical trials is time-consuming, overly expensive, and based on premises that will not apply to the new era of personalized medicine we seek to create. However, Grove's proposed system needs some fine-tuning.

Grove correctly leaves the safety issues to the FDA, but he does not address dosage issues, which should also be determined before distribution. He does not explore how virtual clinical research organizations of the future would monitor issues of compliance and establish fair methods of measuring response. Replacing the heralded phase 3 trial with a self-administered trial would indeed save money and introduce the product much sooner to at least part of the potential market, but pharmaceutical companies would need some shielding of liability to protect them from the increased risks inherent in this plan. Because patients and third-party payers would undoubtedly see the new drugs as experimental, the pharmaceutical companies should be required to offer them at nominal cost.

That said, experimenting (carefully) is exactly what we should be doing. We need to abandon the fallacy of the control group, or the out-of-date comparative product, in favor of historical controls or some other method of assessing the disease. Moreover, no one who is seriously ill wants to be a control. And as diseases are parsed into smaller and smaller subsets—when we find that each person's cancer is as individualistic as his or her face—then all illnesses may become orphans. The days of mass-market clinical trials may soon be over.

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Rethinking Clinical Trials: Biology's Mysteries

A. GROVE TAKES THE PHARMACEUTICAL INDUSTRY to task in his Editorial "Rethinking clinical trials" (23 September, p. 1679). We believe that it is important to place his proposals in a broader context and to examine some of their practical consequences.

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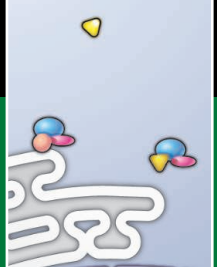
Fear of predation

1353



Plant pathogen immune responses

1354

Grove, a former CEO of Intel, states that $50 billion spent annually to produce about 20 new drugs is "disappointing output." Compared to the semiconductor industry's gains over the past 50 years, the pharmaceutical industry's productivity must seem disappointing. There exists, however, an important distinction between engineering integrated circuits and discovering drugs. The semiconductor industry's realization of Moore's Law has always benefited from a fundamental understanding of solid-state physics. Conversely, we still don't know how living organisms work; new "components," as well as interactions between well-known components, are discovered daily [e.g., (*1*) in the same issue]. This ignorance is the real reason why 90% of drug candidates fail in clinical trials: They simply don't work (*2*). The trial process is doing just what we ask of it.

Grove proposes instead that drugs be approved on the basis of Phase 1 clinical trials, and then, "once safety is proven," the marketplace should sort out which drugs really work by using Amazon-like data mining. His proposal essentially returns us to the days before the 1962 Kefauver Harris Amendment (*3*, *4*), which first mandated data demonstrating drug efficacy. Grove's approach falls short on many levels: (i) Safety is never proven: Taking a drug always entails risk/benefit tradeoffs. Especially as defined by Phase 1 trials, safety is relative; the drug likely won't kill you…immediately. (ii) Large patient populations would be subjected—unethically—to potentially serious side effects before valid statistical evidence of efficacy could be accumulated. (iii) Marketplace-based data gathering will be inefficient at best. Ensuring data quality and patient compliance is difficult even in controlled trials, let alone in a lightly regulated, post-marketing setting.

Finally, how should Grove's "qualified physicians" select, from a substantially increased set, which unproven drugs to prescribe to their patients when faced with volumes of uncertain data? Is "allow[ing] patients to choose between medicines," presumably informed mostly by advertising, any better? Such questions are addressed in Silverman and Lee's still-relevant analysis (*5*).

The merit in Grove's suggestion is not in rethinking clinical trials but in applying computational methods to the analysis of clinical outcomes. Nutritional supplement use, today uninformed by proof of efficacy, could benefit from such analysis—a much safer step forward than dismantling our hard-won regulatory framework. Ultimately, however, focusing on trials and outcomes is limiting: Novel computational methods will alter the very landscape of drug development.

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Primitive Ladder-of-Life Thinking Has Evolved

IN THEIR REPORT "FAKING GIANTS: THE EVOlution of high prey clearance rates in jellyfishes" (16 September, p. 1627), J. L. Acuña *et al*. characterize the lifestyle and features of jellyfishes as more "primitive" than their competitors, sturdy planktivorous fishes. This questionable interpretation traces back to the ladder-of-life thinking of the 19th century, when biologists compared "lower" forms of life with "higher" organisms—species that were supposedly "more perfect" than their little-evolved, simple ancestors (*1*).

However, because coexisting marine organisms, such as the moon jellyfish (*Aurelia aurita*) and the Californian anchory (*Engraulis mordax*), represent the tips of two distant branches of one large tree of life, it follows that *A. aurita* (Phylum Cnidaria) is not "more primitive" or of "lower rank" than the schooling fish *E. mordax* (Phylum Chordata). The life cycle of the moon jelly consists of several phases, including a mobile predatory medusa stage during which the animals sexually reproduce, and a stage of sessile, filter-feeding, budding polyps, generalist feeders that are capable of surviving long periods of starvation (*2*). This mode of development and reproduction is much more complex (i.e., less "primitive") than that of fishes such as *E. mordax*, which reproduce via eggs and predatory larvae that can only survive at high food densities (*3*).

The basic body plans of the earliest jellyfish-like Cnidaria and that of the first marine Chordata originated more than 500 million years ago during the Vendian and Cambrian, respectively (*4*). Since that time, populations of both types of predatory organisms evolved separately in the same marine environment, and today represent living beings of equal rank. The popular view that invertebrates, such as jellyfishes, are primitive animals because they lack our poorly designed backbone (*5*) is inaccurate.

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Response

KUTSCHERA QUESTIONS OUR USE OF THE word "primitive" when referring to jellyfishes as compared with zooplanktivorous fishes. We did not intend to invoke the idea of a "lower rank" in the "ladder-of-life," an old, yet popular, prejudice (*1*). We limited our use of the word to the context of prey encounter mechanisms. We argued that the jellyfish mechanism—stirring water to increase the chance that prey will collide with their collection

surfaces—is less complex than the visual predation by the zooplanktivorous fishes. However, we then showed how the simple mechanism of contact predation is bioenergetically as efficient (i.e., as evolved) as the seemingly more complex visual mechanism. In other words, the main point of our Report could well be used in support of Kutschera's contention.

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CORRECTIONS AND CLARIFICATIONS

News & Analysis: "UNESCO science braces for a big squeeze" by D. Strain (25 November, p. 1045). Gisbert Glaser, a former Assistant Director-General for natural sciences at UNESCO, was described as being concerned that a new engineering technology program might be eliminated. Glaser says he is confident that the program will survive but is worried that it faces large budget cuts. Also, one of Matthew Larsen's job titles was listed incorrectly. He is the Associate Director of Climate and Land Use Change at the U.S. Geological Survey.

Cover: (11 November). The image was a stylized illustration of the globe. Although land boundaries were intended to be schematic, the large island east-southeast of the province of Newfoundland and Labrador was in error. The cover is part of the program materials for the 2012 AAAS Annual Meeting to be held in Vancouver, 16 to 20 February. The map will be corrected in the meeting material.

Policy Forum: "Paying for ecosystem services—Promise and peril" by A. P. Kinzig *et al*. (4 November, p. 603). An acknowledgment should have stated: This document was prepared by participants of a special workshop of the Global Land Project (International Geosphere–Biosphere Programme and International Human Dimensions Programme) held at the Global Land Project 2010, Open Science Meeting, Arizona State University, Tempe, AZ, 17 to 19 October 2010. Support specific to the workshop was provided by NSF (SBE 1025699), National Aeronautics and Space Administration (NNX10AK05G), and National Oceanic and Atmospheric Administration (through the University Corporation for Atmospheric Research).

News Focus: "Fusion power's road not yet taken" by D. Clery (28 October, p. 445). The story incorrectly stated that researchers at the Los Alamos National Laboratory use explosives to crush their fusion target. In fact, they use electrical pulses from the Shiva Star facility at the Air Force Research Laboratory in Albuquerque, New Mexico.

Reports: "Supramolecular linear heterojunction composed of graphite-like semiconducting nanotubular segments" by W. Zhang *et al.* (21 October, p. 340). In Fig. 2, C to F, the scale bars represent 100 nm, not 50 nm.

Reports: "Disentangling the drivers of β diversity along latitudinal and elevational gradients" by N. J. B. Kraft *et al.* (23 September, p. 1755). The location of the elevation transect was incorrectly given as "Carchi, Ecuador" instead of "Braulio Carrillo National Park, Costa Rica." Transects at both locations are reported in reference 14, the source of the data. This change does not affect the Report's conclusions. Additional clarification about accessing this data set has been added to the Supporting Online Material (www.sciencemag.org/content/333/6050/1755/suppl/DC1).

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the past 3 months or matters of general interest. Letters are not acknowledged upon receipt. Whether published in full or in part, Letters are subject to editing for clarity and space. Letters submitted, published, or posted elsewhere, in print or online, will be disqualified. To submit a Letter, go to www.submit2science.org.