Levin Hall,
301 University Boulevard,
Galveston, TX 77555–1013, USA

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NIH Rating System

Although the attempts to standardize the evaluation and scoring procedures of grant applications (E. Marshall, News & Comment, 31 May, p. 1257) are well-meaning, they overlook a major limitation of the current review process: The scores given by individual study section members are not independent measures.

Typically, a grant application is considered in depth by two or three reviewers. They then present their reviews to the rest of the study section, discuss the pros and cons, and publicly announce their scores. Only then does everyone else record a score. Most of the study section members have not read the application under review and may not have a good understanding of the application from the discussion. As a consequence, the vast majority of study section members repeat the score of either the primary or secondary reviewer or split the difference. Without independent evaluations of the applications, statistically manipulating the scores is not justified and will not improve the accuracy or fairness of the process.

At the least, two simple changes should be made. (i) Reviewers should only discuss the merits of the application and should not announce their scoring. (ii) Study section members who feel that they do not have a valid independent evaluation should not be required to submit a score (five independent evaluations are more valuable than 20 repeats). Once independence in scoring is achieved, it would be reasonable to adopt some of the standardized scoring techniques suggested by the Committee on Rating Grant Applications, although reviewers should only score on factors that they feel competent to judge.

The best way to improve the evaluation process would be to increase the number of independent evaluations. The length of proposals should be significantly reduced, and more reviewers should be assigned to each proposal. There is no need for any reviewer to write more than one page of critique, and it is not necessary to designate reviewers as primary, secondary, and so forth, which just encourages everyone to rely on one opinion.

Another way to gain more independent evaluations of a proposal would be to supplement the study section from a large pool of reviewers. Not every reviewer would attend a given meeting, but the outside reviews (two to four) would be read and discussed at the study section (not the scores). Using an outside pool would also allow a better matching of the grant to the expertise of the reviewers and would involve more of the scientific community with the review process.

Our responsibility as scientists is to obtain unbiased estimates of variance in order to evaluate the significance of our findings. It is hard to understand why the same effort should not be made when scoring grant applications. The actual variance in the process may be high, but, if so, we should recognize this and devise a review process that deals with it in a statistically valid way.

Alan R. Gibson
Division of Neurobiology,
Barrow Neurological Institute,
Phoenix, AZ 85013, USA
E-mail: agibson@mha.chw.edu

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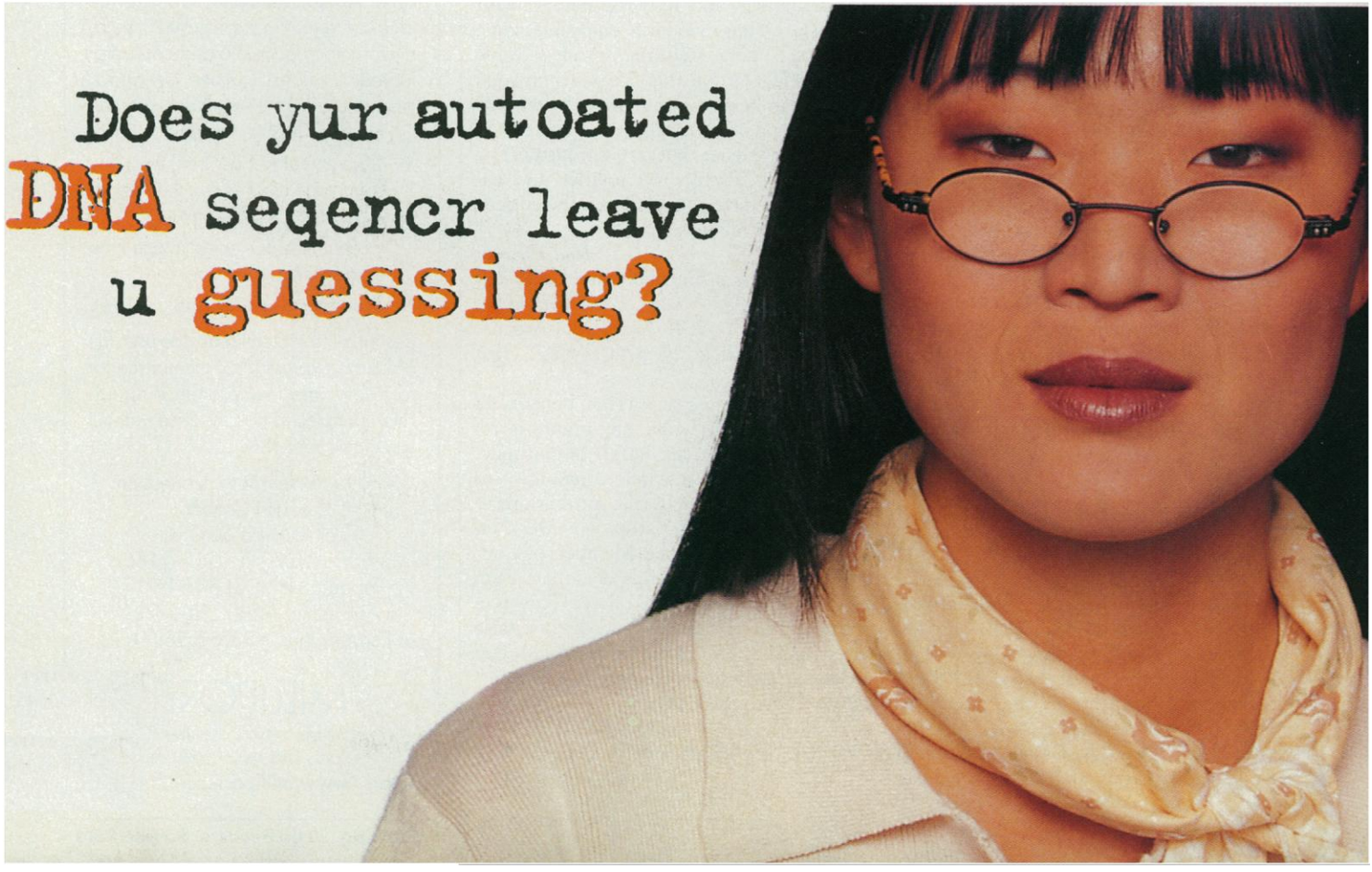
Risks from Low Doses of Radiation: Continued

The three letters published on 3 May (p. 631) challenge some of the statements in my 29 March Perspective (p. 1821), and I would like to address them here. The theme of my



Perspective was a call to arms in questioning and reviewing the basic linear dose-response paradigm for low-level risks. I wanted to open the issue, not single-handedly resolve it.

Jerome S. Puskin and Neal S. Nelson state that "[i]t is widely accepted that carcinogenesis is a multistage process in which a single cell gives rise to a tumor, with mutation of cellular DNA required in one or more of the steps leading to malignancy." This popular theory, however, does not directly translate into a proof to support the linear, no-threshold (LNT) risk model. Although LNT may be attractive and "widely accepted," the hard biological evidence to validate it at very low doses is still lacking. What I questioned was that, because there is a finite distribution of probabilities about the "success or failure" of each of the purported steps from exposure to the onset of cancer, and because that sum is nonlinear, whether cancer risk can be reduced to the first-order kinetics required of the linear model. Furthermore, I did not infer an absolute threshold for effects; I suggested a "practical" one, with such a shallow "slope" that, while the radiation risk may be calculable, it is absolutely negligible; for example, if it is really an S-shaped curve. In fact, it appears that the LNT model "was adapted specifically on a basis of mathematical simplicity, not from radio-biological data, during the period between 1950 and 1964 as the only practicable mathematical approach to estimates of the maximum effects of world-wide fallout from atmospheric weapons testing" (*1*).

My observation that long-term low-level radiation is less carcinogenic than the same total dose delivered all at once is also questioned because I cited numerous animal studies. Puskin and Nelson state that the human studies only show a modest dose rate factor and, further, that studies of the effects of low-level radiation ecological epidemiology have too many statistical and confounding factors. The evidence for a continuum for dose-rate amelioration is compelling (*2*) and should be addressed in an open scientific forum that takes into account the limitations of the data on humans, the issues of temporal extrapolations from animal studies, and modern mechanistic understanding of the damage and repair processes involved.

The example of increasing latency of bone cancer with decreasing dose rate is an interesting example of the role of stochastic processes and how the full extent of the dose-response relationship does not follow linear first-order kinetics. There may be a limit at which point further reduction in rate does not extend latency, but there are other tumor models that seem to show this effect. As a basis for a conservative regulatory policy, linearity is an attractive and simple model; as a true representation of the actual biological facts, especially at low realistic doses, it seems to be only one measure of an upper bound on risk. We should be interested in determining what the actual curve is.

The example of everyone using a 1-inch shoe lift for a year to increase their cosmic ray dose was my extreme example of the folly of collective person-sievert doses as the measure of population risk. I did the unforgivable in forgetting to convert to sieverts in my back-of-the-envelope calculation and overstated the risk by a thousand. The calculation should yield about 1.5 additional cancer deaths, not 1500. Mea culpa! Despite this, it still is an example of carrying risk models too far.

Rudi H. Nussbaum challenges my statement that, at low dose rates, the risk is lower per unit of exposure than when the dose is acute. The National Research Council's BEIR (Biological Effects of Ionizing Radiation) reports use a risk reduction factor of about 2 for low rates, and there may be a broader continuum (*2*). Some deterministic adverse health effects may show worse outcomes at lower rates of exposure but, for radiation-induced cancers following low to intermediate doses, this does not appear to be the case. There are too many animal studies that are too con-

sistent to be discounted because of some limitations in human data assessment.

Donald A. Pierce and Dale L. Preston point out that about 85% of the Japanese Radiation Effects Research Foundation study population have assigned doses below 0.2 sievert. However, 80% of the "excess cancer deaths" were in the 20% receiving higher doses; of the total, 8% received more than 2 sieverts, 23% received 1 to 2 sieverts, and 26% received 0.5 to 1 sievert (thus my calling it *mainly* a high-dose study).

In my Perspective, I did not imply that the data analyses methods of Pierce and Preston might "obscure evidence for a threshold dose below which there is no cancer risk." What I said was the contrary, that (p. 1822) "whether this might be considered a threshold for effects is beyond the purpose of this discussion, especially because uncertainties about individual radiation sensitivity, of dose, and of possible effect of neutrons have not yet been resolved." The dose issue is specifically germane to the survivors at the greater distances, that is, to the lower doses, where dose estimates may be grossly underestimated, and to the disproportionate distributions of relative uncertainties at the lower end of the curve. Again, I am raising the question, not stating that there is a threshold. The case seems still open as to just how linear the response relationship will prove to be when the uncertainties, especially about low doses, are resolved.

Marvin Goldman
Department of Surgical and Radiological Sciences, University of California, Davis, CA 95616–8742, USA

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1. R. D. Evans, A. T. Keane, M. M. Shanahan, in *Radiobiology of Plutonium*, B. J. Stover and W. S. S. Jee, Eds. (JW Press, Salt Lake City, UT, 1972), pp. 522–572.
2. M. Goldman and I. V. Filyushkin, *Chinese Med. J.* **107**, 624 (1994).
3. National Research Council, *Health Effects of Exposure to Low Levels of Ionizing Radiation, BEIR V* (National Academy Press, Washington, DC, 1990).

Letters to the Editor

Letters may be submitted by e-mail (at science_letters@aaas.org), fax (202-789-4669), or regular mail (*Science*, 1200 New York Avenue, NW, Washington, DC 20005, USA). Letters are not routinely acknowledged. Full addresses, signatures, and daytime phone numbers should be included. Letters should be brief (300 words or less) and may be edited for reasons of clarity or space. They may appear in print and/or on the World Wide Web. Letter writers are not consulted before publication.

Corrections and Clarifications

Four lines in box 1 (p. 95) of the report "Homogeneous NMR spectra in inhomogeneous fields" by S. Vathyam *et al.* (5 Apr., p. 92) were incorrect. The correct equations appear below.

$$\rho(t_1,t_2 = 0) = 2^{-N}\prod_i \left\{ 1_i + \tilde{\aleph}\left(\frac{I_{2i} - I_{xi}}{\sqrt{2}}\right) \right.$$

$$\left. - \tfrac{1}{4} I_{xi} I_{zj} \cos[(\Delta\omega_i - \Delta\omega_j)(t_1 + T)]\cos[\gamma G T(s_i - s_j)] \right.$$

$$\tilde{\aleph}^{2n} \overbrace{I_{xi} I_{zj} I_{zk} \ldots}^{2n \text{ terms}} \left\{ \begin{array}{l} \cos[(\Delta\omega_i - \Delta\omega_j)(t_1 + T)]\cos[(\Delta\omega_i - \Delta\omega_k)(t_i + T)] \ldots \\ \times \cos[\gamma G T(s_i - s_j)]\cos[\gamma G T(s_i - s_k)] \ldots \end{array} \right\}$$

$$\times I_{yi} \left\{ \tfrac{3}{2} \sum_{j=1}^{N} D_{ij} \cos[(\Delta\omega_i - \delta\omega_j)(t_1 + T)]\cos[\gamma G T(s_j - s_i)] \right\}^{2n-1}$$

Figure 4B (p. 1937) in the report "Requirement for the adapter protein GRB2 in EGF receptor endocytosis" by Z. Wang and M. F. Moran (28 June, p. 1935) was printed too darkly. The correct figure appears below.

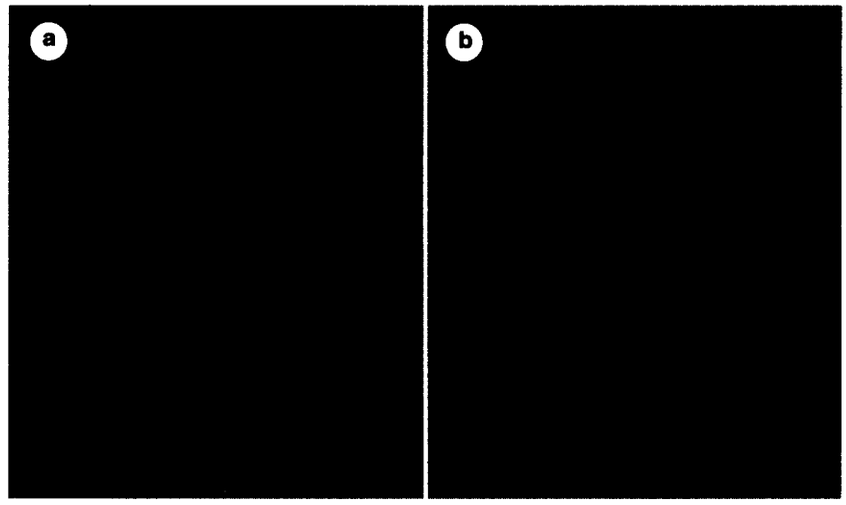

Figure 2 (p. 1793) in the report "Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct" by R. J. Nudo *et al.* (21 June, p. 1791) was printed too darkly. The correct figure appears below.