LETTERS
edited by Etta Kavanagh

Declines in Funding of NIH R01 Research Grants

FOR MANY YEARS, THE NATIONAL CAUCUS OF BASIC BIOMEDICAL Science Chairs, an organization of medical school scientific faculty leaders, has followed U.S. NIH data on the likelihood of investigator-initiated unsolicited R01 research grant applications being funded (1–3). Research supported by these grants, which are the mainstay of research by medical school faculties and other research institutions, has permitted exploration of new approaches to understanding health and disease and development of therapies to treat illness.

We have collected data (6, 7) on the fate of “unamended” (unsolicited) R01 applications. The unamended R01 represents the original application and does not consider resubmissions. NIH classifies R01 applications into type-1 (new) and type-2 (renewals). Revision and resubmission of initially rejected type-1 applications improve the likelihood of eventual funding by a factor of approximately two (4, 8), with smaller increases for rejected type-2 grants. However, each revision of a rejected application delays by close to a year the time required before support can be approved and research initiated. For type-1 applicants, this is a slow, uncertain process that often leads to career reevaluation and change by otherwise successful professional contributors. For an ongoing and previously approved type-2 research activity, rejection casts major doubt on eventual continuation and frequently results in breaking up teams of highly trained personnel. Therefore, success rates for funding initial applications are of primary importance. It is encouraging that the review process itself may begin to accelerate.

The likelihood of funding type-1 and type-2 unamended, unsolicited applications reached a low-point in fiscal year (FY) 1993 and 1994: approximately 12% in each year for type-1 applications (9). For type-2 applications, success rates were 39 and 37%, respectively (2). Thereafter, success rates of unamended type-1 and type-2 R01 applications improved somewhat, peaking between FY 1999 and 2001 (4).

Despite the doubling of the entire NIH budget between FY 1999 and FY 2003, success rates did not increase (4, 5) (see table).

Since FY 2002, success rates have dropped steadily. In FY 2005, the decline was precipitous. Although the total number of applications has increased annually since FY 2002 (see table), not only success rates, but also total number of grants awarded and total dollars committed persistently decreased. For type-1 grants, an overall success rate of 9% has been calculated for FY 2005 (10). Peer review cannot discriminate among and accurately select only 1 of 11 meritorious applications. FY 2006 data are not yet available, but because the total NIH allocation for that period has been less than the biomedical inflation index, a trend toward further diminished support of R01 applications is evident.

Particularly surprising and regrettable is the continuing erosion in the allocation for total R01 annual funding of new unamended applications. This decreased from $510 million in FY 2002 for type-1 grants to $351 million in FY 2005 (see table). These dollar figures represent less than 1% of the entire NIH budget. Of similar concern is the 38% decrease in total number of unamended R01 applications awarded during this period for new applicants (type-1), even though submissions increased 24%. Major reductions are also evident in renewal applications for competing ongoing investigations (type-2).

This issue raises serious concerns about the present and future of U.S. biomedical science because the R01 grant is such an essential contributor to, and index of, scientific innovation. Recent discoveries have provided enormous new opportunities to better understand and treat disease, and we must take advantage of these breakthroughs. In addition, the country’s economic future depends on U.S. leadership in providing new scientific and technical discoveries. Also, failure to provide adequate funds for biomedical research discourages the brightest young people from choosing scientific pursuits.

H. GEORGE MANDEL1,2* AND ELLIOT S. VESELL2

1Department of Pharmacology and Physiology, The George Washington University School of Medicine and Health Sciences, Washington, DC 20037, USA. 2Department of Pharmacology, Pennsylvania State University College of Medicine, Hershey, PA 17033, USA.

*Chairman, National Caucus of Basic Biomedical Science Chairs
†To whom correspondence should be addressed. E-mail: phmhgm@gwumc.edu

References and Notes
6. Kindly provided by Office of the Director, Office of Reports and Analysis, Office of Extramural Research, NIH.

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IRBs: Going Too Far or Not Far Enough?

IN THEIR EDITORIAL “MISSION CREEP IN THE IRB world” (9 June, p. 1441), C. K. Gunsalus and colleagues point out the frustration many have with an increasingly regulated Institutional Review Board (IRB) process that places all human subject research in a fishbowl. However, I see no evidence that the IRBs are neglecting their duties for thoughtful consideration of ethical questions surrounding the welfare of human subjects because of a focus on procedures and documentation; to the contrary, ethical scrutiny is increasing, not decreasing.

Of far greater concern, however, is the contention that IRBs are overstepping their bounds (mission creep) by taking into account issues such as research design and conflicts of interest. Those are precisely the issues that they should examine for human subjects’ protection. I have seen experimental designs in IRB proposals that are so flawed and poorly conceived that even if the agent under study worked exactly as hypothesized, the clinical trial would not reveal it. No human subjects should be recruited to participate in such a trial.

Conflicts of interest are of vital concern to IRBs. One only needs to read the recent Wall Street Journal revelations about atrial fibrillation ablative studies in which some of the clinical researchers failed to reveal to either the IRB or the patients, through informed consent, that they had a clear financial conflict of interest. This type of “omission” potentially places human subjects in jeopardy and raises the issue of egregious research misconduct.

THE EDITORIAL ON “MISSION CREEP IN THE IRB world” (C. K. Gunsalus et al., 9 June, p. 1441) struck a raw nerve. As a scientist approaching retirement after 32 years of research, director of a small nonprofit research institution, and member of two IRBs in the past decade, I now advise students to think twice about getting involved in human research.

I do a great deal of multi-institutional research. It is nearly impossible to deal with a dozen IRBs that review the same protocols when each responds in contradictory ways. Two years ago, one IRB insisted that we could not do what we proposed, and the other IRB involved insisted that we had to do it or they would not approve it. The funded study died. Ten years ago, IRB issues consumed 3 to 5% of my time. Now they consume about 30%.

There is, to my knowledge, not a shred of evidence that the ballooning bureaucracy of IRBs has reduced the number of adverse events or saved a single life. I share the authors’ concern that the focus on minor details has diverted discussions from substantive to trivial. It is also diverting scarce funding from research into indirect costs and discouraging talented young scientists from doing human research.

THOMAS M. VOGT
Center for Health Research, Hawaii, Kaiser Permanente, 501 Alakawa Street, Honolulu, HI 96817, USA.

Response
WE ARE PLEASED THAT THE RESPONSES TO our Editorial about IRB mission creep share a strong commitment to protecting human subjects of research. Vogt articulates issues at the center of our concerns: research delayed, deferred, or never attempted; ever-growing costs; trivialization of review; and diversion of resources (1).

Felten questions whether IRBs are focusing on form over substance. There is a grow-
ing body of evidence that IRB review, particularly in multicenter trials, is costly and inconsistent and tends to focus on minor matters with little bearing on participant safety (2). For example, Rogers et al. report on IRBs demanding changes that are inconsistent with federal regulation (3). There is also ample, and growing, evidence that some IRBs are going astray and that the costs of review are swelling: Sugarman and colleagues have estimated that IRB operating costs range from $170,000 to almost $5 million annually per institution, depending on the volume of research reviewed. They found a median cost of $740,000, although it is thought that these costs are generally underestimated (4, 5).

This increase in costs, however, is often unrelated to better or more consistent protection for subjects. For example, Green et al. document that the costs of securing IRB approval from 43 sites for a 2.5-year multisite observational study totaled 24% of one year’s budget and 13% of the total budget. However, “One site exempted it from review (although it did not qualify for exemption), 10 granted expedited review, 31 required full review, and one rejected it as being too risky to be permitted… Twelve sites requested, and two insisted upon, provisions that directly increased the risk to participants” (6, p. 214). Similarly, Humphreys et al. document that 16.8% of the total costs of an eight-site observational trial were devoted to IRB interactions (7) but observed that there was no visible effect on human subject protection. The essential procedures of the study never changed substantially, despite exchanges of over 15,000 pages of material among the nine sites.”

Finally, we are not against assessment of conflicts of interest, but we believe that there are bodies already constituted at most universities and medical centers better suited to this work. Letting these groups do their job will reduce diversion of IRBs from their core ethical mission.

It is time for all those concerned to find a way to join forces and seek improvements in our ethical systems. We are actively seeking a forum for a consensus conference. Responsible researchers everywhere should be attending to the conduct of IRBs and doing everything possible to buttress their ethical review and minimize their busywork.

C. K. GUNSAUS, EDWARD M. BRUNER, NICHOLAS C. BURBULES, LEON DASH, MATTHEW FINKIN, JOSEPH P. GOLDBERG, WILLIAM T. GREENOUGH, GREGORY A. MILLER, MICHAEL G. PRATT (MEMBERS OF THE CENTER FOR ADVANCED STUDY ILLINOIS IRB STUDY GROUP)

University of Illinois at Urbana-Champaign, IL 61820, USA.

References
2. R. McWilliams et al., JAMA 290, 360 (2003).

CORRECTIONS AND CLARIFICATIONS
News Focus: “A landscape too far?” by T. Siegfried (11 Aug., p. 750). On page 751, the story stated that physicists’ calculations overestimate the vacuum energy by between $10^{10}$ and $10^{12}$ orders of magnitude. The correct figures are between 60 and 120 orders of magnitude. The photo caption on page 751 misidentified Burton Richter as a theoretical physicist. He is an experimental physicist.

Reports: “Crystal structure of a divalent metal ion transporter CorA at 2.9 angstrom resolution” by S. Eshghi et al. (21 July, p. 354). On page 357, in the acknowledgments (reference 29), the PDB accession code was omitted: The structural data have been deposited in the Protein Data Bank with accession code 2iub.

Research Articles: “Crystal structure of the low-pH form of the vesicular stomatitis virus glycoprotein G” by S. Roche et al. (14 July, p. 187). The Protein Data Bank accession number, 2cmz, for the glycoprotein structure described was omitted from the acknowledgments (reference 39).

TECHNICAL COMMENT ABSTRACTS

COMMENT ON “TRANSITIONS TO ASEXUALITY RESULT IN EXCESS AMINO ACID SUBSTITUTIONS”

Roger Butlin

Paland and Lynch (Reports, 17 February 2006, p. 990) showed that in Daphnia pulex, the ratio of amino acid replacement to silent substitution in the mitochondrial genes is higher in asexual lineages than in sexual lineages. If base-composition bias is maintained by selection, it too should alter following transitions in reproductive mode. Analysis reveals no such change in the genomes of D. pulex.

Full text at www.sciencemag.org/cgi/content/full/313/5792/1389b

RESPONSE TO COMMENT ON “TRANSITIONS TO ASEXUALITY RESULT IN EXCESS AMINO ACID SUBSTITUTIONS”

Susanne Paland and Michael Lynch

Asexual populations experience a reduction in the efficiency of selection when compared with sexual populations. Because asexual lineages of Daphnia pulex exhibit no consistent change in mitochondrial base-composition bias, Butlin suggests that this bias is not maintained by selection. On the basis of frequencies of polymorphic directional base changes, we suggest that it predominantly reflects mutation bias.

Full text at www.sciencemag.org/cgi/content/full/313/5792/1389c
Comment on "Transitions to Asexuality Result in Excess Amino Acid Substitutions"
Roger Butlin (November 21, 2014)
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Editor's Summary

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