

Biomedical Gerrymandering

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Competitiveness is a constant in the history of the extramural funding program at the National Institutes of Health. The first NIH invitation for extramural applications was a letter sent to medical school deans in 1946, by Cassius Van Slyke and Ernest Allen, Public Health Service employees who were handed several million dollars to distribute. “We have limited funds available for research purposes. If you have investigators who need these funds, let us know by return mail.” They received more than a thousand requests; Allen later referred to the request for applications as “the most naïve letter ever to emanate from the national government in Washington.”¹ Although the intensity of competition for research-grant money varies with funding cycles, nearly every applicant must deal with the potential for rejection. Understanding how funding decisions are made is critical for the research community, and is equally important for those who make science policy.

The NIH extramural grant program, the largest of all sources of funding for American biomedical research, is undergoing a massive reorganization that includes the reapportionment of fields funded. Though this restructuring has made no national headlines, its implications are profound. The structure of the NIH peer-review process reflects national priorities, and shapes the questions researchers ask.

Peer-review review

NIH is required by law to carry out technical and peer reviews of research proposals. The mechanism for performing these reviews, however, is not mandated. The NIH review process is overseen by what is now known as the Center for Scientific Review (CSR; formerly the Division of Research Grants). Each grant proposal to NIH is read by one of more than one hundred study sections, groups of 20 scientists who work in or near the field of the proposal. In the most recent structure, the study sections were clustered into 19 Integrated Review Groups (IRGs), each being responsible for a broad area of science. The study section makes a recommendation as to whether the grant should be funded, and in so doing is supposed to consider only scientific merit. The final decision, however, is separated from review and is the responsibility of the individual institute Advisory Councils. The Councils can take into account policy and financial concerns.

Although this system seems straightforward, complaints about it are as old as the extramural program itself. The most substantive concerns about the system had to do with referral, the process for assigning a grant to a particular study section,

and with the criteria used for ranking grants. Having a grant land in the wrong study section can be fatal; additionally, there was a general sense that the study sections as they are currently constituted are generally out of date.

The first concern was addressed indirectly in 1997 by Harold Varmus, then director of NIH. During a reconsideration of criteria for scoring grant proposals, Varmus defined five—significance, approach, innovation, investigator, and environment—that continue to be used. Discussion continues as to how the criteria should actually be utilized. For example, currently only a global score is given. Should the criteria be scored separately? Scored separately and then averaged? Some researchers worry that simply having a list of criteria in no way guarantees that any reviewer is paying attention to them, or that criteria that are easier for scientists to judge (e.g., approach) are given undue weight. One of the most general criti-

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cisms of peer review is that in fact no one knows what is being scored. While this frequently sounds like the whining of rejected investigators, anecdotal evidence suggests that for many, the system is a mystery—even to those who administer it.²

The second concern, the makeup of study sections, is currently being addressed by the Center for Scientific Review. This is an ongoing process, in some ways truly an experiment in policy, and no doubt there will be multiple changes to the structure and procedures that will define the new review process. The major body responsible for outlining changes to the Center for Scientific Review is called the Panel on Scientific Boundaries for Review. It is headed by Bruce M. Alberts, president of the National Academy of Sciences and so is known as the Alberts Committee. The initial proposal, submitted in January 2000, received significant feedback from the biomedical community, especially from those who thought that their areas had been slighted or ignored. In the current iteration there are 24 Integrated Review Groups, up from 21 in the initial proposal. Workers in virtually every field that was absorbed into a new IRG provided some sort of comment to the committee. For example, under the committee’s original proposal, AIDS and AIDS-related research would have been absorbed by at least two IRGs: immunology, and infectious diseases and microbiology. After much comment from AIDS researchers, AIDS and AIDS-related research retain their IRG.

¹ See Robert Cook-Deegan, *The Gene Wars: Science, Politics, and the Human Genome* (W.W. Norton, 1995), p. 136, and Barbara Culliton, “NIH: The Good Old Days,” *Science* 244 (1989): 1437.

² R. Finn, “Who Serves?,” *The Scientist* 9 (1995): 1.

Researchers in other areas also campaigned to have their fields remain in independent IRGs.³ Similar dissension might be expected as CSR attempts to form new study sections within the IRGs.

At the NIH—as in America—aging is considered a disease state: development and aging are in a single IRG. Four of the review groups focus on cellular or subcellular processes (bio-

Current (Old) Integrated Review Groups	Phase 1 (New) Integrated Review Groups
Biochemical Sciences	Discontinued; dispersed to many IRGs
Nutritional & Metabolic Sciences.	Discontinued; dispersed to many IRGs
Cell Development & Function	{ Molecular Approaches to Gene Function Molecular Approaches to Cell Function & Interactions Biology of Development & Aging
Biophysical & Chemical Sciences [†]	Biological Chemistry & Macromolecular Biophysics
Genetic Sciences [†]	Fundamental Genetics & Population Biology
Cardiovascular Sciences	{ Cardiovascular Sciences Hematology
Endocrinology & Reproductive Sciences [†]	Endocrinology, Metabolism, & Reproductive Sciences
Immunological Sciences [†]	Immunology
Infectious Diseases & Microbiology [†]	Infectious Diseases & Microbiology
AIDS & AIDS-related Research ^{††}	AIDS & Related Research
Oncological Sciences [†]	Oncological Sciences
Musculoskeletal & Dental Sciences	{ Bone, Muscle, Connective Tissue, & Skin Renal & Urological Sciences
Pathophysiological Sciences	{ Digestive Sciences Pulmonary Sciences
Risk, Prevention & Health Behavior	Risk, Prevention, & Health Behavior
Social Sciences, Nursing, Epidemiology & Methods	Health of the Population
Behavioral & Biobehavioral Processes	Behavioral & Biobehavioral Processes
Surgery, Radiology & Bioengineering	{ Surgery, Applied Imaging, & Applied Bioengineering Fundamental Bioengineering & Technology Development

[†] Old and new IRGs clearly related; may be somewhat altered in scope.
^{††} In the original iteration, AIDS and related research would have been distributed among other IRGs such as Immunology and in Infectious Diseases and Microbiology. Following the first round of comments it was retained.

Organization

The restructuring of the Integrated Review Groups and study sections could be an exciting reform of the review process, or yet another step in the “diseasification” and further fragmentation of the research enterprise. Of the 24 IRGs, 11 are focused on particular organs or systems, including 3 IRGs for neuroscience. Following the NIH’s absorption of the National Institute of Mental Health, the National Institute of Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism, new neuroscience IRGs were created to accommodate the research from those institutes. For the moment these remain relatively intact. Although it could be argued that the healthy state of these systems will be studied as well, nearly all of the interesting work is in understanding disease states. The review groups for infectious diseases, for AIDS, and for oncology clearly are focused on disease mechanisms.

chemistry and biophysics; gene function; cell function; and genetics and population biology). Though no disease tilt is given any of these, almost any step in normal metabolism can lead to disease if dysfunctional. Three of the review groups are concerned with behavior, risk prevention, and healthy populations. As with neuroscience, these IRGs were created following the absorption of Alcohol, Drug Abuse, and Mental Health Administration by NIH, and for now will remain intact at the study-section level. Whether these will concentrate more on public health or on gene-seeking remains to be seen. The final two IRGs encompass applied bioengineering, fundamental bioengineering, applied imaging, technology development, and surgery. Although these are general in scope, they do concern themselves with curing or palliating disease. Undoubtedly, in order to understand disease states it is useful to understand healthy states, and vice versa. But the categorization by (potentially diseased) organ is even more apparent than under the current regime.

At the same time, it is curious that clinical research remains spread out over many IRGs. There are strong indications that

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³ B. Agnew, “NIH eyes sweeping reform of peer review,” *Science* 286 (1999): 1074-1076.

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particular study sections within review groups will comprise clinical studies separated from basic research. Still, there has been a general sense that clinical research has suffered in funding, perhaps particularly because it is difficult for basic scientists to evaluate clinical research, even with the assistance of practitioners. Whether clinical research will continue to suffer within the new IRGs will be closely watched by both the clinical-research community and patient groups.

Science and society weigh in

The National Institutes of Health has been criticized both for being too disease- and organ-oriented and for not being disease-oriented enough. Taxpayers, among others, obviously would like NIH-funded scientists to find cures for diseases. Clearly, the reorganizing of review groups and study sections is meant to change the focus of reviews. What change is hoped for and what is achieved? The Alberts committee invoked four goals: to provide a home for the review of all science that is relevant to contemporary biomedical research; to have each IRG be sufficiently coherent to allow its external advisory group of scientists to judge the entire scope of its science; to have research related to a given system or disease, including fundamental studies, be reviewed within a single IRG or a related set of IRGs; and to have the organization be flexible enough to adjust to the rapid changes in scientific opportunities expected in the years ahead.⁴ These are laudable goals for the Center for Scientific Review. But how will they affect investigator-initiated, curiosity-driven research? Will it make for better preventives, cures, and palliatives? Is it good for science and for society?

Working scientists are not known for their long view of the research enterprise. Whether a particular system of graduate-student admissions, of tenure review, or of federal funding is thought to be successful tends to depend on whether or not the individual scientist is benefiting from the system. Evaluating the success of a new grant review system will be especially hard, because the societal outcomes will not be apparent for many years.

Fulfilling the promise of basic, investigator-driven research will require changes in the culture of research. Inspection of the paper titles of any journal reveals the amount of overlap in the kinds of experiments done and the model systems pursued. Whether this would result in improved societal outcomes may depend on how seriously the clinical study sections are finally allowed to pursue bona fide health-related research. The setup of the new IRGs says it will; the reality check will be in how the grants emanating from the study sections are funded.

The jewel in the crown?

The National Institutes of Health holds a special place in American culture. It is one of the few federal agencies—perhaps the only one—that has the respect and good wishes of both the executive and legislative branches of the federal government, of both major political parties, and of the American people. And whining aside, scientists generally hold NIH in high regard. Whose opinion, then, should carry the most weight as critical decisions about the NIH are made?

Funding is perhaps the most critical decision. With a budget fast approaching \$20 billion a year, some individuals and groups, including disease lobbies, government officials, and watchdog groups are beginning to be concerned that NIH-funded scientists as a whole have not been held accountable for outcomes, Government Performance and Results Act notwithstanding. But even the presumptive internal workings of NIH, including the process of grant distribution, should concern everyone, not just grantees, because it may determine what kinds of research get funded.

After receiving commentary from the research community, members of the Alberts panel and Harold Varmus himself made a point of saying that the reorganization would not result in anything radically different in terms of retail peer review. But if criteria other than straight scientific merit are eventually coupled to the broader definition of what sort of works fit together in a single study section, the result could be the funding of riskier, more imaginative, and, perhaps, less disease-oriented and more generally applicable work.

Alternatively, the new IRGs could become even more pointed and less interested in considering work outside their immediate interests. This is especially likely to happen as new institutes are added. Somewhat incongruously, and contradicting the desires of many NIH administrators including the former director Harold Varmus, the U.S. House of Representatives approved the creation of a new institute, the National Institute of Biomedical Imaging and Bioengineering, which could pass this year, or shortly thereafter.⁵ There are always researchers who will believe that their fields are underfunded, underrecognized, undervalued. And although “interdisciplinary” is a nice buzzword, few researchers actually understand or engage in true interdisciplinary research. It is hard to imagine exactly how broader, deeper IRGs can have any real positive impact on research if the NIH becomes balkanized, which seems to be the goal of the current Congress and of at least some researchers: “Having an institute will allow imaging and bioengineering researchers to chart their own course,” propo-

⁵ HR 1795. See K. Fisher, “Imaging Institute Picks Up Momentum,” *Science* 289 (2000): 2015-2017.

⁴ <http://www.csr.nih.gov/bioopp/select.htm>

nents argue.” For example, Reed Dunnick, who also testified before the Commerce panel: “Cancer people have no interest in talking to the lung people” about their findings. “Nothing short of an institute will be effective in stimulating and coordinating biomedical research to the extent that is needed.”⁶ No doubt many less politically-savvy groups of researchers feel the same way about their fields.

At the same time, we do not have enough experience to know what structure would best assure positive outcomes for their stakeholders—meaning funded research for scientists, new diagnostics and therapies for the public. Varmus’s experiment could determine whether the disease & organ approach is better or worse than more general approaches. At the very least, it is more honest, or at least more consistent, with stated NIH policy. The vast majority of researchers submitting grants to NIH fill out form PHS 398, which asks the investigator to “mak[e] reference to the health relatedness of the project.”

⁶Fisher, *ibid.*

Two human genome projects

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lose by not making it. The genome institute’s budget was secure whether or not they finished the genome first, but Celera exists in the world of venture capital and bottom-line priorities. Had they been beaten by NIH, it could have meant disaster.

Thus we end up with the group hug splashed across the pages of *Nature* and *Science* and the banner headlines in the dailies. Venter and Collins, who grind their teeth when they smile at each other, paint a portrait of mutual admiration. At the White House, Collins spoke first, indicating both his less spectacular achievement and his position of greater security. Venter followed, flashier, less substantive, and further from the President.

Corporate sponsorship is relatively new to biomedicine. Chemistry has always had strong support from the private sector, and astronomy has long maintained a balance between federal and philanthropic support. But the long-term goal in biomedical research is unique among the sciences: improved public health. The shift from federal toward corporate sponsorship begins to substitute the bottom line for the life line. Zinder argues reasonably that big technology is what private companies do best; the government, he says, should sponsor smaller-scale, higher-risk, more exploratory projects. So the shift toward corporate sponsorship encourages biotechnology at the expense of curiosity-driven research. This tends to make it easier and faster to do targeted research on big-name diseases, and to make it nearly impossible to do the kinds of longshot studies in backwater fields that have provided so many unexpected breakthroughs.

That poses a dilemma for a true basic researcher: respond honestly—“None”—or make something up?

Concern or even backlash from researchers might be expected. In these good economic times even scientists can, to some degree, take their business elsewhere; corporate sponsorship of biomedical research is growing rapidly. Certainly the intent of the reorganization is neither to endanger basic research nor to direct it all toward ultimately curing disease. But this restructuring indicates that the NIH and the Center for Scientific Review have recognized at some level that as successful as curiosity-driven research may be at the output level, scientists must work for their most important supporters: taxpayers and citizens. The Constitution confers no right to a specific job (ask any Pacific Northwest lumberjack). If there is a sincere societal desire and willingness to push for more results from basic research, then the result may be some decrease in the basic research program, and it would be worth it.

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Yet the flow goes both ways. Although Venter is long departed from academic science, he still must play by some of its rules. The primary currency in basic research is credit. Publication in *Nature* a week before your competitor can mean prizes, students, promotions. Venter’s credibility depends on maintaining standing in the scientific community. It must put him at odds with his investors at times, but he has little choice but to maintain at least the grudging respect of his potential customers.

One hopes that the two genome projects—public and private—will complement each other. Certainly, the competition has speeded up the sequencing thus far. But I will be anxious to see which of three outcomes will result. Will Celera’s data be so good that it will give a competitive advantage to companies and universities that purchase subscriptions? If so, the gap between rich and poor in research biology will widen considerably. Or will the NIH data, freely available to anyone with an internet connection, be good enough that few will bother to subscribe to Celera? This would strike a blow at technology transfer that might in fact lead to cuts in the NIH budget. Or will some middle ground be found, in which Celera and NIH collaborate in good faith, sharing data but leaving room for Celera and other companies to offer gene annotations, power-search engines, and other profitable value-added services while ensuring the open access to data on which science depends?

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