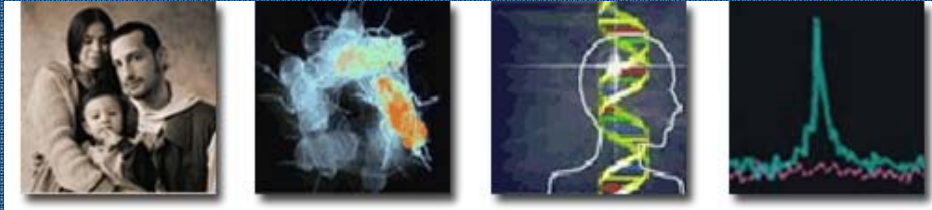


Special Update

From the NIMH Director



Fulfilling the Mission During the Lean Years

The National Institute of Mental Health (NIMH) is about to celebrate its 60th birthday. As a healthy 60-year-old, NIMH is certainly not thinking about retirement. This is a time of unprecedented promise for mental health research. In the next decade, with the help of powerful new tools from genomics and neuroscience, we look forward to advancing the **“four Ps” of biomedical research**: improved **prediction of disease** via biomarkers, developing **personalized treatments**, effective **preventive strategies** for disorders like post-traumatic stress disorder and schizophrenia, and **participation** from the diversity of people and settings involved in mental health care.

For many grantees, this moment of great promise comes at a time when NIMH funding seems to be waning. As someone said to me recently at a public meeting, “You’ve given us a roadmap for progress, but is there any gas in the car?” In this editorial, I want to clarify the NIMH budget picture, describe how we are responding during these difficult budgetary times, and share some of the tough choices we are making to balance the pipeline of new researchers with the payline for new research projects.

“You’ve given us a roadmap for progress, but is there any gas for the car?”

How much gas is in the car?

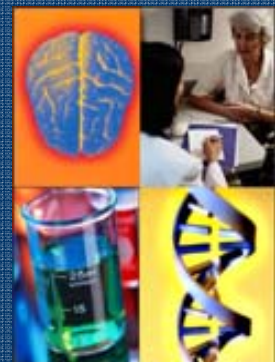
From fiscal year (FY) 1998 until FY 2003, the budget of NIMH increased 80 percent to \$1.34 billion, including \$175 million for research on AIDS. This large increase allowed the Institute to invest in a number of areas of science — including large-scale practical clinical trials and the translational Conte Centers — and to expand its research training efforts. However, from FY 2003 until FY 2006, the budget was nearly flat. In the fiscal year that ended September 30, 2006 (FY 2006), the NIMH budget was \$1.39 billion, an increase of less than 4 percent from FY 2003.

During this nearly flat three year budget period, biomedical inflation increased by at least 3.5 percent per year. But even more important than inflation has been the unprecedented increase in research capacity across the nation. Universities have invested more than \$15 billion in infrastructure (mostly new construction) since 1998¹. Over the past decade, research training programs have expanded the pipeline. As a function of the increase in research infrastructure and investments in research training, the capacity surged just as the growth in the budget for research slowed. The number of research project grant (RPG) applications increased from 2,210 in FY 2003 to 2,757 in FY 2006, an increase of 25 percent when the budget grew less than 4 percent.

What’s Inside

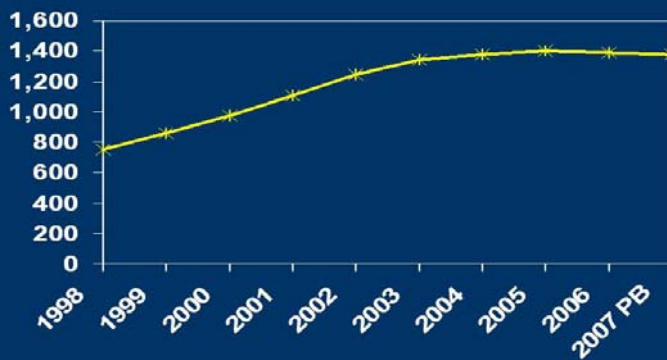
- *Fulfilling the Mission During the Lean Years*
- *NIMH Intramural Program*
- *Public Trust & Public-Private Partnerships*
- *Clinical Trials Networks*

Prepared for the 2006 Annual Meeting of the American College of Neuropsychopharmacology



NIMH
National Institute
of Mental Health

National Institute of Mental Health
Appropriation
FY 1998 – 2007 (Dollars in Millions)



This mismatch of supply and demand was foreseeable in FY 2003. When we modeled the post-doubling period for NIMH, we considered that the yearly Institute budget would likely not keep up with inflation, but that the churn of previously funded grants would help to cushion the hard landing of flat budgets after double-digit budget increases. In any year, roughly 70 percent of the NIMH budget is committed to the out-years of multi-year grants. By projecting when these grants would end and the likelihood that only a fraction (roughly 30 percent) would be re-funded, we could mathematically model the lean funding picture following 2003. Of course, we only know our Congressional appropriation one year at a time. The challenge was to manage the Institute budget, knowing that the demand was increasing but not knowing exactly how tight the budgetary supply would be.

What is the best way to manage this mismatch of supply and demand?

NIMH established a few fundamental principles. Most important, the Institute focused on advancing its public health mission: reducing the burden of mental illness and behavioral disorders through research on mind, brain, and behavior. Each of our decisions about funding

strategies has been made with this urgent mission in focus. We believe that the investigator-initiated R01 grant is critical for fulfilling this mission. Given that mental illnesses are complex brain disorders, we believe that translational research is essential and team science will make some of the most rapid progress. Additionally, we realize that research on services and implementation must be part of our effort to reduce the public health burden since people with mental disorders are often outside traditional health care settings and there are profound disparities in mental health care.

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Over the past three years, NIMH has used several strategies for managing the mismatch of supply and demand. Our first strategy, begun in FY 2004, was to reduce the average costs of competing grants to maintain support of roughly the same number of competing RPGs as the prior year. The average cost of a competing RPG increased 32 percent between FY 1998 and FY 2003 to \$309,000. By reducing the average cost, NIMH was able to pay more competing RPGs in spite of a flat budget and the relatively low

turnover of funds available from grants that were ending. We also reduced the rapid expansion of out-year commitments, keeping more of the budget available for new scientific opportunities.

While this strategy helped to maintain the number of newly competing RPGs in FY 2004 and FY 2005, it did not work as well in FY 2006. Responding to the expectations of reductions in awards, requested budgets for competing RPGs increased. Even with an average 10 percent reduction in awarded budgets, the average cost for a competing RPG in FY 2006 increased to \$324,000. Meanwhile, the number of applications continued to escalate, probably exacerbated by reduction in size of awards. The 25 percent increase in applications from FY 2003 until FY 2006 ensured that the success rate (defined as number of RPG applications funded divided by the number of applications received) would fall. Indeed, the average success rate for an NIMH RPG (such as an R01, R03, or R21) decreased from 27.1 percent in FY 2003 to 19.7 percent in FY 2006.

Our second strategy, begun in FY 2005, was to emphasize more heavily Institute and program priorities when making funding decisions. The tradition at NIH has been to pay grants in priority order, based on scores from study section. The payline is the cut-off priority score for payment (<http://www.nih.gov/about/researchresultsforthepublic/successrates.pdf>). In general, grants at or below the payline were paid, contingent on concurrence of the National Advisory Mental Health Council (NAMHC). Grants have two levels of review: the study section scores for scientific merit followed by the NAMHC, which oversees the integrity of peer review and advises the Director about funding based on portfolio balance, significance of the science, and fit with Institute priorities.

...NIMH identified a range of specific scientific opportunities and three vulnerable areas that needed to be protected in a changing funding climate: innovation, new investigators, and translational research.

Beginning in 2003, as we looked ahead to tough budget times, we realized we would need to update and clarify Institute priorities. Development of these priorities involved input from various stakeholders — patients and their advocates, physicians/scientists and their professional societies, Congress, and the NAMHC, which includes members from academia and the public. In addition, the NAMHC convened workgroups to recommend priority areas for future investment. Through this process, NIMH identified a range of specific scientific opportunities and three vulnerable areas that needed to be protected in a changing funding climate: innovation, new investigators, and translational research. The specific priorities for the Institute and each of its extramural divisions are described on our website (<http://www.nimh.nih.gov>).

How can we ensure that the available funds are used for these priority areas?

Paying strictly by priority score was not the answer. Study sections review applications and assign scores based on scientific merit, without regard to changes in the priorities or portfolio balance within any specific Institute. It is the role of program staff, the NAMHC, and Institute leadership to integrate this valuable information from peer-review with the specific priorities, the need for portfolio balance, and budget

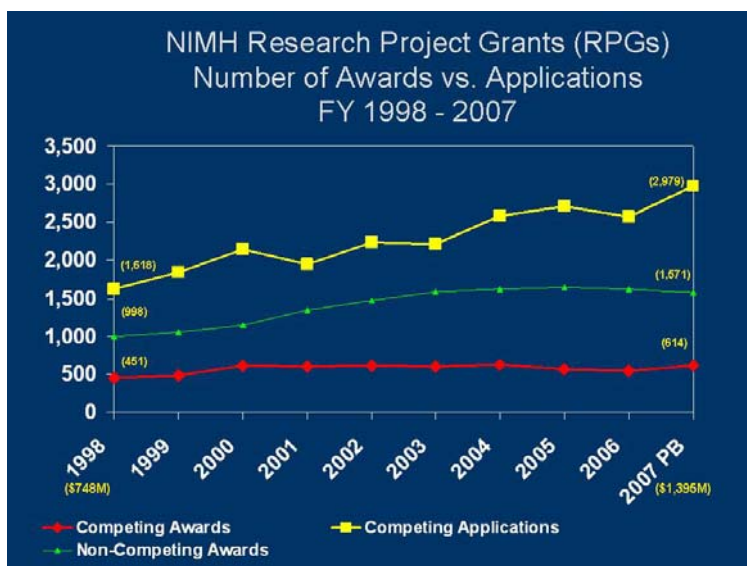
constraints to optimize funding decisions.

In order to emphasize more heavily our priorities, we assume that all grants up to the 20th percentile are scientifically meritorious. NIMH funds have been able to support, at least through FY 2006, roughly three-fourths of these applications. Rather than paying this three-fourths in strict percentile, program staff, in concert with the NAMHC, evaluates all applications up to the 20th percentile, identifying those most closely aligned with research priorities and makes recommendations for payment accordingly. As a result, a 19th percentile application from a new investigator with an innovative approach that is likely to advance scientific discovery in a high priority area may be paid before a 9th percentile application from an established investigator where the science is less in tune with priorities.

Indeed, NIMH strives to support nearly all new investigators scoring in the top 20th percentile, even during this difficult funding climate. To ensure that we support the most innovative ideas, program staff recommend for payment applications below and even beyond the 20th percentile that can be supported for one year — to get the research started and to get a better sense if the innovation will lead to discovery.

Our third strategy in many ways has been the most difficult. NIMH has had one of the largest commitments to research training of any of the 27 institutes and centers at NIH. We are proud of our pipeline that supports diverse investigators from undergraduate research training through the mentored K (research career awards) programs.

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In FY 2004, looking at the expanding commitments to training and the prospect of a shrinking capacity to pay new research grants, it was obvious that our pipeline was no longer balanced with our payline. By training more young investigators every year while funding fewer grants, we were creating a situation where NIMH provided funds to train a new generation of scientists but would not necessarily have the resources to provide grants to them in the future.

To alter this course, we implemented a seven-year plan (FY 2004 – FY 2010) to scale back on training, reducing training from 10.5 percent to 8.6 percent of the NIMH budget (the NIH average is approximately 7 percent). An analysis of different training mechanisms convinced us that T (institutional training) mechanisms were yielding fewer subsequent NIMH or NIH grantees than F (individual fellowship) mechanisms. Likewise, the mentored Ks were successful at yielding subsequent R01 investigators, but they had proliferated to an extent that the out-year commitments were draining our ability to support new competing mentored K awards.

While recognizing that subsequent NIH funding was not a perfect measure of success, the data were compelling enough to suggest reducing the number and size of T awards, while preserving F awards, and scaling back the number of K awards. The plan for K awards was altered a bit by the NIH issuance of the Pathway to Independence Award, the K99/R00 mechanism, which provides two years of mentored K support prior to three years of independent research

support (<http://grants2.nih.gov/grants/guide/pa-files/PA-06-133.html>). In FY 2006, we funded 56 competing mentored Ks, down from 80 in FY 2004. The total number of mentored Ks (competing and non-competing) in this period changed from 379 to 362.

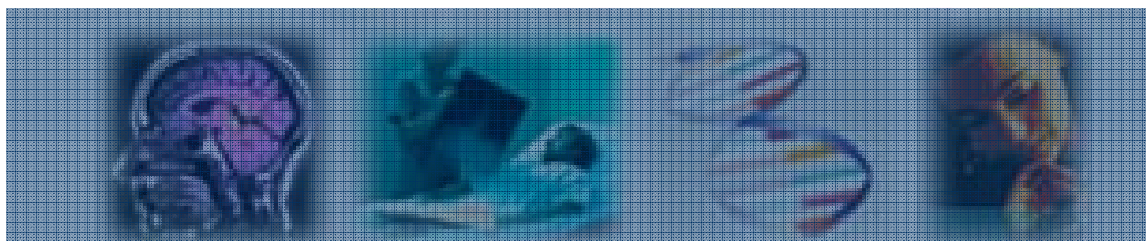
Of course, the research training question is not only how many but in what areas of science? Our field is in the middle of a profound cultural change. Many clinical trainees emerging from psychology, social work, and psychiatry programs do not have the basic science and/or interdisciplinary skills needed to address the kinds of translational research questions that are among the Institute's priorities. Similarly, many of the basic science trainees do not have an appreciation for the complexity of mental disorders needed to address the Institute's priority to build an integrated science of brain and behavior for advancing discovery in mental health research and treatment.

The Institute needs a new generation of scientists with skills bridging areas such as genomics and cell biology, developmental neuroscience and childhood psychopathology, and clinical trial expertise and behavioral science to address health disparities. As with research grants, research training needs to be strategic, with a clear vision of the skills and experiences needed to make the basic, translation, clinical, and mental health services breakthrough discoveries in the next two decades.

We recognize that this strategic

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focusing of the research-training portfolio has been and will continue to be painful. Some excellent, junior research scientists will not receive their K awards and many will not receive funding with a first K application. Note, however, that even though the reduction from 80 to 56 new K awards each year looks drastic, the success rate in FY 2006 for mentored K awards was 27 percent, well above the success rate for RPGs. For the T awards, additional research training programs developed through the NIH Roadmap and the Neuroscience Blueprint provide valuable opportunities for support and can help soften the landing. And most important, by shifting funds to research grants and putting a priority on funding research grants from new investigators, we ensure that those receiving support for research training are more likely to receive subsequent support as independent investigators.



Conclusion

There are no painless paths through these tough financial times. We have an urgent, critical mission, and we have clear priorities for fulfilling this mission. I have described three strategies: (a) controlling the average size of RPGs, (b) emphasizing Institute priorities in funding decisions, and (c) balancing the research training pipeline with the RPG payline. These are experiments we are trying in an effort to fulfill the NIMH's mission during this time of flat Institute budgets. Each has been guided by the data we have on past performance and our best projections of future funding. Like all experiments, we can only control some of the relevant variables.

We have used the NIMH website and the e-publication *Inside NIMH* as

community newsletters to keep everyone abreast of the challenges and the changes. Going forward, we solicit and welcome your comments and suggestions through the NIMH website at nimhwebmaster@mail.nih.gov. There is no way to know how long we will be in this season of sub-inflationary budgets and there is no magic that we can offer for alleviating the pain, but we can promise to be responsive, transparent, and focused in our approach to our public health mission.

ⁱ Zerhouni, E.A. (2006). NIH in the post-doubling era: Realities and strategies. *Science*, 314, 1088-90.

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The NIMH Intramural Program

The NIMH Intramural Research Program (IRP) has long been a flagship for the Institute. Established to respond to emerging public health needs and to support the most innovative science, the IRP in the 1970's and 1980's ushered in a golden era of discoveries in neuropharmacology, treatment development, and translational research. While the IRP's proportion of the total NIMH budget has decreased from 23.1 percent in 1985 to 11.3 percent in 2005, the program is still one of the Institute's most important investments. Indeed, the IRP FY 2006 budget of \$160 million makes it one of the largest mental health research institutes in the world.

The IRP of today has little in common with the program of previous decades. Over the past 10 years there has been a substantial turnover of faculty with the loss of many of the founding fathers (including Seymour Kety, Julius Axelrod, and Louis Sokoloff) as well as many of the second generation of leadership (Frederick Goodwin, Richard Wyatt, Michael Brownstein, Robert Post, and Thomas Wehr). Over the past year, an entirely new leadership team has taken the helm. Alcino Silva, from UCLA, is the new Scientific Director, and Donald Rosenstein is the new Clinical Director. An ambitious training program, headed by Barry Kaplan, ensures that fellows learn to write competitive grants as well as getting thorough training in research ethics and methods. And a new cadre of tenure track investigators has joined the program, bringing a wave of enthusiastic, young clinical neuroscientists (Andreas Meyer-Lindenberg, Christopher Baker, Kuan Wang, and Zheng Li) to the program.

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In place of Building 36, which has been demolished, and Building 10, which mostly has been closed, the IRP resides with several other neuroscience institutes in the new Porter Neuroscience Research Center and in the new Clinical Center, a state-of-the-art research hospital.



Where is the program headed?

The IRP has put its focus on translational research. Large efforts in schizophrenia (Daniel Weinberger) and mood and anxiety disorders (Husseini Manji) are developing and applying genomics and imaging tools to solve some of the most complex problems in medicine. Longitudinal developmental studies (Jay Giedd and Judith Rapoport) are redefining the trajectory of brain development. Responding to a new public health demand, the IRP has launched an ambitious program in autism (Susan Swedo) including efforts to develop new treatments. New collaborative programs with extramural investigators have been developed to expand the IRP clinical research effort.

All of these efforts have three goals: (a) to make progress on the most disabling mental disorders, (b) to train and support the brightest and best young

investigators interested in clinical neuroscience, and (c) to develop the tools and resources that can serve scientists around the nation.

The IRP has always been a place for high-risk/high-yield science. Like the extramural program, there has been a financial squeeze with laboratory operating budgets cut 12 percent in 2005 and not increased in 2006. Currently the program is in a period of change, with unprecedented scientific opportunities; unique scientific resources for cell biology, neuroimaging, and genomics; and extraordinary new talent. After a major turnover of leadership, the IRP is poised to usher in a new era of discovery for mental disorders.

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- To train and support the brightest and best young investigators interested in clinical neuroscience, and
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Public Trust in NIMH and Public-Private Partnerships

One of the most common urban myths I hear as I travel is that NIH scientists cannot have any contact with their colleagues in industry. This is simply not true.

There was a period from June 2004 until August 2005 when, prompted by disturbing revelations from a Congressional oversight hearing, NIH conducted an in-depth review of paid consulting arrangements between its employees and pharmaceutical and biotechnology companies. This review ultimately led to the issuance of new ethics regulations, which were finalized in August 2005 and set clear limits on stock ownership, outside activities, and awards for NIH employees. The fundamental principle of these new guidelines is to more explicitly separate public service from private gain. Importantly, while NIH scientists are prohibited from engaging in outside activities with industry for compensation, they are still permitted to collaborate with industry as part of their "official duties." This means that interaction with colleagues in industry happens on government time as part of a scientist's regular, government activities, not as outside

consulting for money. Official duty activities with industry require approval, but they are recognized as essential for NIH to fulfill its public health mission.

In addition to new guidelines to clarify how NIH scientists can interact with their colleagues in industry, NIH has been building public-private partnerships via the Foundation for the NIH (FNIH). FNIH is a Congressionally-established private, not-for-profit group that brings industry, government, and academia together for exciting new collaborations.

For example, in one recent project, the Genome Association Information Network (GAIN), Pfizer, Perlegen, and Affymetrix worked cooperatively to support genotyping for whole genome association studies of several thousand schizophrenia, bipolar, major depressive disorder, and ADHD samples from the NIMH Genetic Repository.

FNIH also hosts the Biomarkers Consortium, a partnership of NIH, Food and Drug Administration, Centers for Medicare and Medicaid Services, and

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industry to support pre-competitive studies of biomarkers. Recently, the Biomarkers Consortium accepted a project to develop genomic biomarkers predicting SSRI response using data collected during the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. The Biomarkers Consortium promises to be a new source of funding for pre-competitive research of interest to NIH, industry, and the academic community.

NIMH is working to ensure that the field of mental health research, which has been challenged recently by public skepticism, makes strides to achieve the highest levels of public trust. Scientific progress requires that NIH, academic, and industry scientists collaborate, recognizing that each sector has a unique contribution to public health. Working through FNIH and under new conflict of interest rules, it is our hope that the best collaborative ideas can be supported in a transparent, open arena.

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Expediting Public Mental Health Science through Clinical Research Networks

Networks of clinics and clinicians have been supported for over four decades by the NIH as a means of supporting clinical trials. NIMH is joining this effort by providing *infrastructure* support to maintain three large networks of investigative clinical teams that have evolved from the large practical clinical trials of interventions for major depressive disorder (Sequenced Treatment Alternatives to Relieve Depression — STAR*D), for schizophrenia (Clinical Antipsychotic Trials of Intervention Effectiveness — CATIE), and for bipolar disorder (Systematic Treatment Enhancement Program for Bipolar Disorder — STEP-BD) in adults. Each *new study* initiated on the Networks *requires separate funding* from public or private sources or a combination of public/private support. Because these Networks already provide rapid and efficient access to nationwide clinical sites and staff that are well-trained, efficient, and experienced, the Networks are ideally suited for addressing the kinds of real-world “effectiveness” questions that require large and diverse samples and aim to impact clinical practice.

NIMH is currently reviewing the process for funding future research on the NIMH clinical trials Networks. The goal is to encourage an open and competitive arena to elicit the best science to improve clinical practice, while at the same time maximizing the efficiency of the conduct of that science.

The overarching principle is that the Networks will provide the infrastructure for research designed to improve the mental health of the public and to help inform clinicians. To accomplish this, research must be informed by broad scientific and public input. The Networks are poised to address the public mental health questions that cannot and are not being addressed by non-government entities, as well as research questions that are beyond the scope and timeframe of the R01 process.

Starting in December 2006, NIMH will issue a Request for Information to solicit suggestions for the most important

research directions and projects for the Networks **from a broad range of investigators, stakeholders, and individuals living with mental illnesses.** These suggestions, whether from the Networks' principals or from the wide range of public and research stakeholders, will be reviewed by a workgroup of the National Advisory Mental Health Council (NAMHC). The workgroup will report its findings on top research areas and approaches to the full NAMHC for consideration.

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RESEARCH = HOPE

National Institute of Mental Health

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For More Information...

<http://www.nimh.nih.gov>
<http://intramural.nimh.nih.gov>