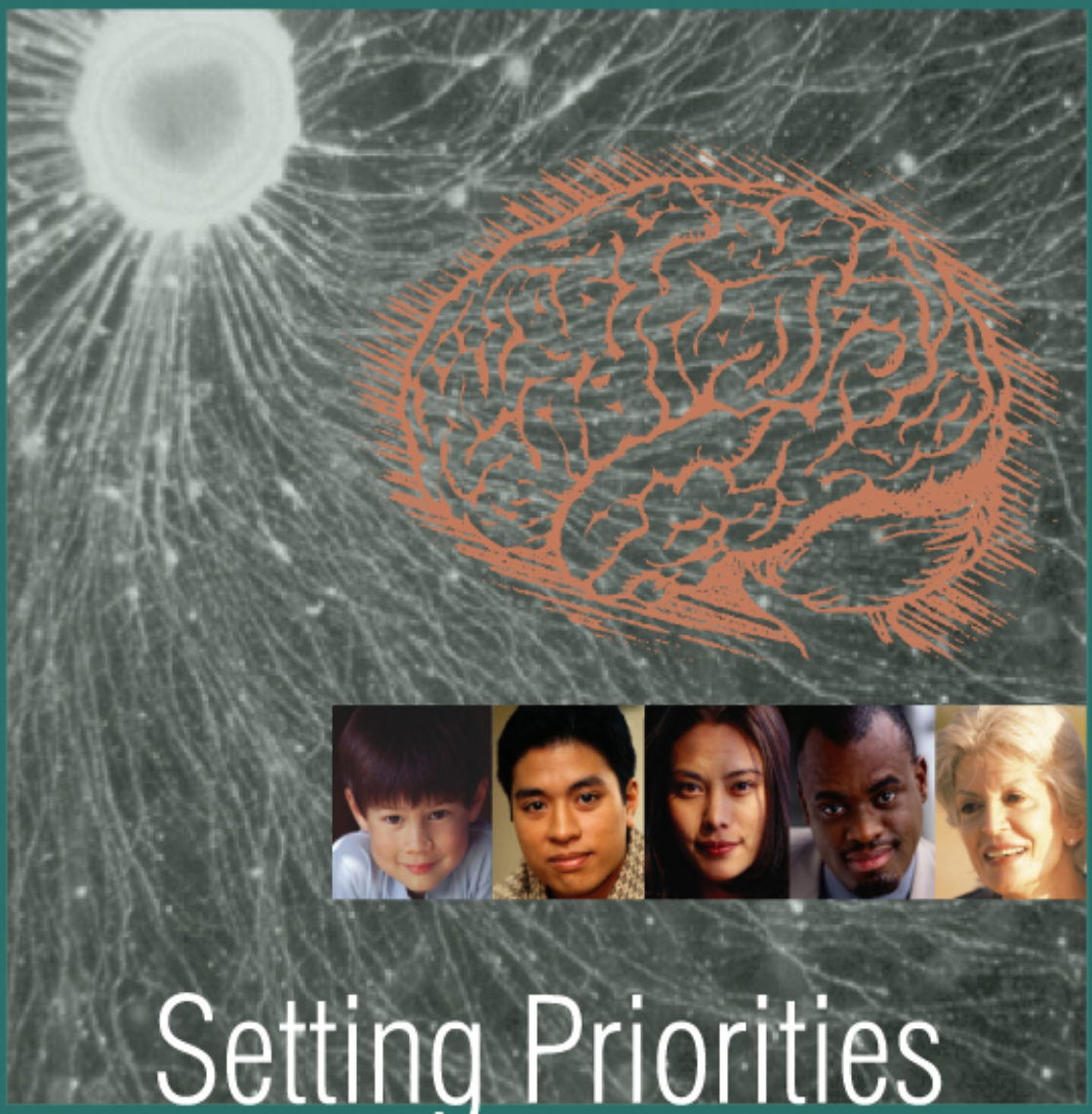

Setting Priorities for Basic Brain & Behavioral Science Research at NIMH

Report of the National Advisory Mental Health Council's Workgroup on Basic Sciences

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES NATIONAL INSTITUTES OF HEALTH NIMH National Institute of Mental Health

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PREFACE

The mission of the National Institute of Mental Health (NIMH) is to reduce the burden of mental illness and behavioral disorders through research on mind, brain, and behavior. In pursuit of this mission, NIMH supports and conducts the highest quality science across the public health spectrum, from basic research investigating the mechanisms underlying behavioral and neurobiological phenomena, to targeted research on the prevention and treatment of mental illnesses. It also supports research on finding optimal ways of providing the best treatment and services available directly to the community.

The basic science portfolio of the NIMH spans multiple levels of analysis - from molecular, to cellular, to systems, to individual and social behavior - and is contained within the Division of Neuroscience and Basic Behavioral Science. Within the division, three branches are responsible for the support of basic research covered in this review. The Molecular, Cellular, and Genomic Neuroscience Research Branch supports fundamental research on the elucidation of the genetic, molecular, and cellular mechanisms underlying brain functions. The Behavioral and Integrative Neuroscience branch supports research targeted at understanding the normal operation of brain structures and functions and how these may be dysregulated in psychiatric disease. The Basic Behavioral Science branch supports research that delineates the principles of healthy behavior in order to better understand the behavioral differences that characterize mental disorders. In recent years, NIMH's investment in basic science has led to great advances in a number of areas, including a better understanding of the genetic and cellular mechanisms underlying neural function, advances in uncovering the neural networks and systems involved in certain aspects of cognition and behavior, and the impact of social and environmental factors on individual function.

NIMH is committed to maintaining this progress through its continuing support of the basic sciences related to mental disorders. However, in an era of decelerating budgetary growth, it becomes necessary to set clear priorities in order to ensure maximal impact of the Institute's investments. To assist in setting these priorities, the NIMH sought the advice of the National Advisory Mental Health Council (NAMHC), which in turn established a workgroup to conduct a thorough review of the current portfolio and to make recommendations for predicting which areas are most likely to yield discoveries that ultimately will benefit people with mental disorders. The council sought advice for membership on these workgroups from several professional societies representing both the behavioral science and the neuroscience communities. It developed a distinguished roster of highly respected researchers and leaders in the field.

The NAMHC Workgroup on the Basic Sciences of Mental Health was established in December of 2003. The Workgroup was charged with reviewing the existing NIMH portfolio in molecular, cellular, and behavioral neuroscience, basic behavioral, and basic cognitive science, and asked to consider three factors to guide its deliberations and assess the impact of the research: the relevance to the mission of NIMH; the potential traction of areas of science - those that are ripe for making rapid progress; and, the innovative nature of the research areas in question. From this charge, three fundamental issues emerged:

1. Which areas of research are poised to begin integrating findings across levels of analysis from the molecular to the behavioral? And of these, which are most likely to have relevance to elucidating the disturbances seen in mental and behavioral disorders?

2. Which areas of basic research are most readily translatable into clinical science to address issues of etiology, prevention, treatment, and service provision for the mentally ill, and conversely, which areas are less likely to translate into questions of clinical importance?

3. Which research approaches are most likely to advance our knowledge?

The initial meeting of the Workgroup took place on January 13, 2004, and involved presentations by NIMH staff on the existing basic science portfolio as well as a general discussion about the overall approach to assessing impact. The Workgroup formed two subgroups: one to focus on the basic molecular and cellular portfolio, the other on the basic behavioral and behavioral neuroscience portfolio. Members then individually reviewed the portfolio and suggested areas of potential high-priority/impact that are not now adequately addressed, and areas that appeared to be over-represented in the portfolio.

Each subgroup then held its own meeting in order to reach consensus. The first to meet was the Molecular and Cellular Neuroscience Subgroup on February 3, 2004. The Basic Behavioral and Behavioral Neuroscience Subgroup met on March 3, 2004. On March 31, 2004, the Workgroup held its final meeting to formalize recommendations for this report. This document reflects the consensus of the Workgroup, aimed at providing the NAMHC with the group's advice concerning priority-setting in the NIMH basic research enterprise.

PROLOGUE:

The basic sciences are critical and essential for fulfilling NIMH's public health mission of reducing the burden of mental and behavioral disorders through research on mind, brain, and behavior. It is often very difficult to forecast accurately where great advances are likely to emerge; therefore it is important that NIMH maintain its commitment to a wide range of basic sciences. Progress in reducing the burden of mental illness will require that the field elucidate the causes, develop better diagnostic tests, refine classification of disorder phenotypes, develop better treatments, and enhance prevention efforts - all goals requiring a strong fundamental science base. The goal of this Workgroup is to recommend ways to sharpen the impact and focus of the basic science portfolio such that it may even better serve the mission of the

Institute. In working toward that goal, the Workgroup remained cognizant of the likely budget context for the next few years and therefore strove to identify truly high priority areas for increased emphasis and areas where reduced effort or refined focus might best serve NIMH and its mission.

In conducting its review, the group identified several over-arching principles that guided its work.

Principle One: Basic brain and behavioral research should be undertaken in the service of the public health mission of NIMH. Basic science questions that are most central to understanding the potential causes, treatment, and prevention of mental illness and behavioral disorder should be the highest priority.

Principle Two: Basic research that integrates or translates across levels of analysis - from genetic, to molecular, to cellular, to systems, to complex overt behaviors - should be given high priority. It is increasingly evident that an integrative systems approach is achievable and that more of this type of research is needed. This is not to say that research within each respective level of analysis is not also extremely important. However, there is now far too little integrative research and thus it should be given markedly increased emphasis in the future.

Principle Three: Research and training that is interdisciplinary in nature should be more heavily emphasized in the basic science portfolio. The leading edge of much of biomedical research involves integration of physical, biological, behavioral, and social science. Thus, to accelerate cross-level-of-analysis integration and to strengthen the focus of basic research on topics central to the public health mission of the Institute, there is a great need to increase the amount of interdisciplinary research and ensure a future cadre of appropriately trained scientists able to work successfully in interdisciplinary teams.

Principle Four: Numerous studies in the past have uncovered the profound effects of the physical, social, cultural, and economic environments on individual behavior; more recent advances now indicate that it may be possible to examine the effects of environments on behavior at both the molecular and integrative systems levels. This emerging field of epigenetics has received relatively little attention at NIH, as the tools for analysis of such interaction have not yet been solidified. The Workgroup considers it time to invest more in developing the tools that will allow intensive study in this area, given that most mental disorders appear to involve or result from such dynamic processes over time.

Cross-cutting Issues

In applying these guiding principles to the evaluation of the portfolio, the Workgroup also identified several crosscutting themes that apply to many aspects and topical areas within the portfolio and be given high priority. One of these themes is sex and gender differences. Serious psychiatric disorders in both children and adults are often more common in one sex than in the other. This should serve as a point of entry for the study of the underlying mechanisms that modulate the differential vulnerability of each sex to particular disorders in terms of brain function and behavior.

In addition, the study of individual differences in basic behavioral and neural processes should be given high priority, since it holds one key to understanding vulnerability to psychopathology.

Similarly, adolescence and earlier phases of development should be given high priority. These are periods in which expression of certain psychiatric disorders increases, or periods during which environmental influences on brain function may be particularly apparent, yet little is known about the neural, physiological, and behavioral changes that underlie these developmental shifts and vulnerabilities.

The development of more appropriate animal models for specific aspects of mental disorders was also considered an important issue for the Institute in the coming years. The Institute should seek clearer justification for the choice of a particular species for the questions being asked. In addition, more emphasis is needed on studies that examine the performance of animals in natural or naturalistic settings in order to accurately study natural variation among individuals.

I. Areas for Increased Emphasis

The Workgroup identified several areas of research that are particularly ripe for increased NIMH investment at this time. These are areas of both special need and special opportunity, based on recent progress or on the emergence of novel tools that will enable new questions to be asked and answered. These typically are areas that the Workgroup also considered to be currently under-represented in the NIMH portfolio.

1. **Emotion** - Key features of many mental illnesses and behavioral disorders involve altered emotional regulatory processes. While excellent basic brain and behavioral research is being supported on this topic, the Workgroup identified two key areas that should be emphasized; the neurobiology of emotion, mood, and motivation; and, the interaction of emotion and cognition.

    - Investment should be made in studies on the molecular neurobiology and neural circuitry of the brain's regulation of emotion, including its adaptations to stress, including social stress, with an emphasis on understanding adaptations and sequelae of chronic stress exposure on affective and appetitive neural circuits.

    - Research on the interaction of emotion and cognition is important for understanding the mechanisms of action of psychological treatments, such as the effects of cognitive behavior therapies on mood disorders. Related to this is research on emotion regulation, self-regulation, and cognitive control of emotion. Research on emotion-cognition interactions should be pursued from the perspective of numerous levels of analysis, with work conducted on any one level being informed by the relevant work of the others.

2. **Development** – Research on human and animal development spans the domains of several NIH Institutes. For NIMH, therefore, basic science studies of developmental processes across the lifespan should have compelling rationale and relevance to understanding the etiology, treatment, or prevention of mental illness. The field is too

broad for NIMH to provide meaningful support across all areas; rather, NIMH should work with other institutes to develop guidelines such that each institute has an appropriate and complementary focus. Within this context, the Workgroup recommends that NIMH supported research should focus on defining the environment's long-term effects on brain and behavior, through activities that might include:

- Studies on periods of rapid neurobiological development in humans, during which the brain is particularly sensitive to context/environment/intervention influences.
- Studies on how neural activity and gene-environment interactions regulate late prenatal development, such as the development of forebrain and limbic systems.
- Later-stage postnatal developmental processes (e.g., formation of neural circuits, post-natal neurogenesis, neuronal replacement, synaptogenesis, regressive processes).
- Creating better animal models (including non-mammalian) of these stages of development.
- Studies exploring intersections of social and cognitive functioning with neurobiological development.

3. **Social interactions** - The ability to engage in harmonious social relationships, handle conflict and aggression, and receive and offer nurturance are central to mental health, and aberrations in these behaviors and processes are fundamental in the development, definition, and course of psychopathologies. Valuable research on social behaviors and processes relevant to mental illness is now being supported and should continue to be supported. It also is now possible to include work on the molecular, cellular and systems levels to better understand the neurobiology of social interactions. The Workgroup recommends that NIMH invest in this new area of research that integrates social processes and behaviors with brain functioning, in both human and non-human species. One such example is the study of the brain circuitry involved in social attachment, which can provide new avenues for the development and assessment of behavioral and pharmacological interventions.

4. **Neural circuits** - The advent of new tools and technologies provides a special opportunity to advance understanding of the structure and functioning of brain circuits underlying healthy and abnormal behavior. NIMH now supports an array of research using those tools. However, the Workgroup considered it particularly timely to increase efforts in this domain. Efforts toward this goal should include:
   - Greater investment in cellular imaging tools and increased application of these tools to in vivo models, as well as to human brain imaging.
   - More studies on the neural circuitry involved in psychotropic drug action and complex behaviors.
   - Better understanding of synaptic mechanisms, particularly integration of multiple synaptic inputs.
   - Greater use of molecular and genetic approaches to trace complex neural circuits.
   - Occurrence and significance of neuronal replacement.

5. **Sex and gender differences and mechanisms -** Relative risk levels for many psychiatric disorders are markedly different in males and females. Males are at higher risk for early onset disorders such as autism and attention deficit/hyperactivity disorder, whereas females suffer higher rates of major depressive disorder, anxiety disorders, and eating disorders. Rates of schizophrenia are similar in males and females but age of onset, response to treatment, and range of symptoms vary as a function of sex and gender[1]. These robust sex and gender differences in the human population require further investigation and are mirrored in animal models where sex and hormonal status exert profound influences on neurobiology and behavior. This should serve as a point of entry into the study of underlying mechanisms that mediate vulnerability to neuropsychiatric disorders by providing a principal variable, be it hormonal, genetic or psychosocial. Systematic comparison of males and females developmentally and in adulthood, using both human and non-human subjects, will provide novel insights into normal and aberrant neural functioning as it relates to mental disorders and could lead to the development of more effective therapies for males and females.

6. **Intracellular signal integration** – Only a small subset of proteins expressed in the brain has yet been characterized. A more complete understanding of the complex networks of neuronal and glial proteins is needed to provide the foundation of knowledge required for the eventual elucidation of the causes of mental illnesses and the development of novel interventions. More specifically, the actions of first messengers such as neurotransmitters and neurotrophins on neuronal and glial function occur through the regulation and interactions of intracellular signaling pathways. More investment is needed in studies of these cascades, including the regulation of gene expression. Specific opportunities include:
   - Understanding how multiple signal transduction pathways interact to produce integrated cellular responses.
   - Use of non-mammalian model organisms to delineate intracellular pathways implicated in cellular phenomena relevant to the mammalian brain.

II. New and Improved Research Tools

This is an era where advances in technology are driving science as much or more than the reverse. To make those tools particularly useful for studies related to NIMH's mission, however, requires that they be adapted to the basic and clinical science of mental disorders. Thus, in reviewing the basic science portfolio, the Workgroup identified several areas where careful investment in the development and adaptation of research tools and techniques would serve as catalysts for advancing the basic science of mental disorders. These developments could and should be pursued collaboratively with other institutes since the products could be used in related domains as well.

1. **Appropriate animal models -** A major challenge for advancing the basic science of mental disorders is the development and use of animal models appropriate to the understanding of normal and abnormal human behavior. Effective models must take

[1] Sex differences are those that are largely biological in origin; gender differences refer to the influence of environment, experience, and how a person is addressed by social institutions.

into account the idiosyncrasies of individual species and be able to produce reliable results that can be replicated across laboratories**.** In some cases, the most commonly used laboratory species may not be the best choice; therefore, more consideration and justification is needed for the choice of a particular species for the specific question being asked. More emphasis is also needed on naturalistic animal models and housing conditions that harness the natural variation among individuals. Suggestions for specific model species include:

- Mouse behavior: development of tests that would allow greater delineation of molecular and cellular mechanisms of complex mouse behavior relevant to psychiatric disorders.
- Genetic tools for the rat: including rat genomics and transgenic-knockout methodologies.
- Targeted investment in non-human primates: they offer the unique opportunity to study highly complex cognitive and emotional functions.
- Use of non-mammalian model organisms (e.g., worm, fly, fish, bird): to delineate intracellular pathways implicated in cellular phenomena relevant to the mammalian brain.

2. **Ligand development -** Increase investment in the development of ligands to promote basic neurobiological discoveries and to ultimately facilitate drug discovery efforts. This is not to say that NIMH should become involved in drug discovery per se; rather, that ligand development should be directed toward creation of pharmacological tools for validation of novel targets and for new brain and cellular imaging agents. Both would help translate molecular and cellular discoveries into the behavioral and clinical realms.

3. **Computational models -** Models that are neurally plausible can provide powerful new insights into the dynamic interactions within and among neural systems. More work is needed that simulates the effects of varying neurotransmitter levels and/or neuromodulatory influences in neurocomputational models of issues such as cognitive control, attention, and decision-making to shed light on underlying causes of behavioral abnormalities found in psychiatric illnesses

4. **Standardization of behavioral tools –** NIMH should invest in the development of stimulus sets/tasks and process-oriented measures of cognition, emotion, and overt behaviors that can be used across development and across species in research. This does not necessarily imply the identical stimulus sets or tasks across species but rather the development of tasks that reflect the same function. Stimulus sets and measures that can be independently validated will facilitate comparability across laboratories, though their availability must not preclude progress in the development of better and converging measures as fields evolve. The use of variable tools should not be de-emphasized. A set of more standardized behavioral measures that are derived from and informed by neuroscience research, as well as CNS measures themselves, could provide a powerful adjunct to extant treatment studies and could be used as a complement to more traditional outcome measures that rely on self-report or are interview based.

5. **Neuroimaging -** Neuroimaging is a new and promising technique for investigating brain and cognition. The technology continues to improve, as do methods for both anatomical localization and data analysis. NIMH should emphasize studies of neuroimaging that make good use of anatomical information and the latest technological innovations, and which bring together the best of both psychology and neuroscience. There is very little known about the relationship between neuroimaging signals, based on PET or fMRI, and other methods of measuring brain activity, such as c-fos or single unit recording. Increased emphasis should be placed on determining what exactly is being measured with these techniques, and how it may provide insight to emotional, cognitive, and other higher brain processes relevant to mental health and illness.

III. Areas Ready for Refocus

The Workgroup, in considering the full breadth of the current basic portfolio, identified several areas of research that have been very productive but that would also now benefit from an evolutionary shift in focus to have greater impact in accomplishing the mission of the Institute. These areas include:

1. **Aspects of learning and memory –** The portfolio is very extensive in this area. NIMH's research program continues to be one of the great success stories in developing a detailed understanding of the psychological, neural, and cellular mechanisms underlying learning and memory and other phenomena. Because most mental illnesses involve distortions and problems in cognition, learning, and memory, continued strong investment in this area is clearly warranted. It is important now, however, to build on this success and begin to emphasize the integration of learning and memory in terms of brain and behavior, as well as within and across various domains of cognitive function and emotion.

   Examples of this integration are already evident in the portfolio. For example, behavioral research on extinction of conditioned fear has shown that extinction results from a new form of learning, rather than an erasure of the original memory. These insights are now guiding anatomical and cellular studies to investigate this form of inhibitory learning. Similarly, studies of behavioral phenomena, such as conditioned inhibition, have been shown to be a superior way to study fear inhibition, which again is guiding anatomical and cellular studies. NIMH should tilt the focus of the learning and memory area to emphasize research that integrates perspectives across levels of analysis on topics of clear relevance to mental illness, such as studies of both animals and humans; or studies of neuroimaging within a strong anatomical context; and behavioral studies in conjunction with genetic or specific pharmacological manipulations directed at particular circuitry or cell types. In addition, the Institute should emphasize research, both neurobiological and behavioral, that integrates across domains in the cognitive area, such as decision-making, executive function, attention, speed of information processing, language, and social cognition.

2. **Sleep –** NIMH should refocus its portfolio to emphasize mechanistic studies of sleep and its relationship to waking behaviors, and to reduce its investment in simple phenotyping of sleep problems in psychiatric disorders, which has largely been accomplished. Future investigations could include understanding the molecular neurobiology and neural circuitry of sleep, arousal, and attentional states as well as studies of sleep's influence on cognition, memory, affect, and other cognitive and emotional functions in the waking state.

3. **Circadian biology –** It is time to shift emphasis - from studies focusing only on molecular circadian mechanisms, or only on behavioral circadian phenomena, or only on sensory circadian phenomena - to studies of the molecular and neural systems basis of circadian phenomena that relate to aspects of higher brain function and behavior relevant to NIMH (emotion, mood, motivation, cognition, attention, arousal, etc.) under normal and pathological conditions. It would be useful for NIMH to convene a separate workgroup to determine how best to maximize the impact of future research on this topic.

4. **Stress –** Stress is clearly relevant to mental illness and is ripe for neurobiological focus. NIMH should encourage a shift from studying acute stressors, where much research has been conducted already, to more chronic stressors, because the impact of the latter appears to be more relevant. Also, more emphasis should be placed on determining how different forms of stress (e.g., physical, social, emotional) may differ in their behavioral and biological consequences. As stated earlier, more investment is needed in stress and its influence on affect, mood, and cognition. Also relevant to the topic is the study of resilience. Analysis of those who are relatively unimpaired when faced with stress could provide important clues to mechanisms that might be harnessed in the prevention and treatment of stress-related psychiatric illness. Also needed are studies of interventions that protect against or reverse the impact of stress.

5. **Neurotransmitter-signaling systems** - Encourage a shift from extensively studied neurotransmitter-signaling systems to systems that are less well understood and, in particular, how these various systems are integrated and mediate aspects of neural circuitry. As just one example, emphasis should be placed on studies of a novel signaling pathway or on how that pathway interacts, for instance, with the brain's serotonin system as opposed to studies of the serotonin system alone, which has already been extensively characterized.

6. **Prejudice and stereotyping** – NIMH should shape this portion of the portfolio to encourage more transparent relevance to mental health issues rather than focusing on mental representations of hypothetical targets or social groups of less relevance to the Institute's mission. For example, NIMH should encourage studies on the consequences of prejudice and discrimination as chronic stressors; developing interventions for those who are targets of prejudice as well as for those who engage in it; developing interventions for persons with mental illness who are targets of prejudice and stereotyping. In light of the large portfolio in this area, it would be useful for NIMH to convene a separate workgroup to determine how best to maximize the impact of future research on this topic.

IV. Areas Better Served by Other Institutes

Cognizant of current and emerging budget constraints, the Workgroup considered whether some areas within the NIMH portfolio might be less relevant to the central NIMH mission and might also be better served by other NIH Institutes whose missions relate more directly to them. It should be made clear that these conclusions do not reflect a negative view of the quality of these research programs, which is in fact quite high. These recommendations simply reflect the judgment of Workgroup members on their relevance to NIMH's public health mission. Thus, the following are research areas that the Workgroup suggests might fit more appropriately in the domains of other NIH Institutes:

- **Visual and other primary sensory perception and motor processes**
- **Metabolic/thermoregulation**
- **Characterization of the processes of normal development or aging without a compelling argument for the relevance to mental illness or behavioral disorders.**

V. Concluding Remarks

The Workgroup reiterates that the Institute should continue its long tradition of strong support for both basic behavioral science and basic neuroscience.

The Workgroup also recognizes that keeping abreast of the latest scientific developments and maintaining a balanced portfolio – which spans the wide variety of mental health needs inherent in the NIMH mission – in times of increasing budgetary restraint is a real challenge. It is the consensus of this Workgroup that the basic sciences portfolio can be made more relevant to the NIMH mission and portions of it better focused to take advantage of innovative opportunities, particularly through efforts to integrate across levels of experimental analysis.

The group suggests that NIMH Program staff frequently scrutinize the portfolio to identify areas that may become overly subscribed with highly similar grant applications, particularly as an area becomes "hot," and in heavily studied areas, support only those applications offering the most innovative approaches. Staff should also be alert for an excess of grants that may focus on well-established phenomena, paradigms, and methods at the expense of newer ones with potentially higher relevance. Program staff could also regularly provide advice to investigators regarding the current depth of investment in selected research areas. This would inform applicants whether certain scientific areas have already been saturated. In addition, to promote the most pressing mental health needs to the field, NIMH could highlight on its website a description of the areas of relatively high and lower priority to the Institute.

For the basic science portfolio to reflect shifting scientific and public health priorities, it may be useful for NIMH to work with CSR to re-examine the focus and composition of study sections to reflect a stronger translational emphasis and include multiple disciplinary or

levels-of-analysis perspectives. Program staff could help by nominating scientists who have a greater appreciation for translational or cross-levels-of analysis research.

NIMH should try to create ways of fostering and supporting translational research and research training. For instance, the Institute should develop funding strategies explicitly designed to stimulate R01s that bridge different levels of analysis (e.g., imaging work combined with behavioral; animal combined with human work). Where it is tractable, studies that include (or at least are cognizant of) findings from different disciplines could be emphasized. Reducing the segregation of basic and clinical research is essential; investigators working at each level need to become aware of the work at the other levels.

To help make the basic sciences more relevant to clinical issues, training programs for basic scientists should include education on the clinical phenomena of mental illness. (This strategy may also potentially be worthwhile when tried in the other direction: training programs for clinical scientists might include instruction on the basic sciences of mental health.) NIMH might consider adding a requirement to all basic research training grants that trainees be exposed to clinical material. This could be accomplished in the form of a seminar series, grand rounds, patent presentations, short courses, etc.

NIMH may also consider developing educational tools itself: tools for use in the field that give examples, at different levels, of successful translational research. Another possibility is for NIMH to offer short courses at the larger neuroscience and behavioral science annual conferences to showcase translational research.

In conclusion, the Workgroup was impressed with the quality of basic science research in the NIMH portfolio. This made the task of evaluating the portfolio intellectually interesting as well as greatly challenging. Given the current state of science and the existing fiscal climate, however, the Workgroup considers it timely and very important that NIMH find ways to modify the basic sciences portfolio to take advantage of the recommended Areas for Increased Emphasis and Areas Ready for Refocus. In so doing, strong support for the basic sciences will be maintained and the impact of the portfolio will be enhanced in terms of relevance, traction, and innovation for reducing the burden of mental illness.

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Appendix 1:

National Advisory Mental Health Council Workgroup: Setting Priorities for the Basic Brain & Behavioral Science Research at NIMH

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Appendix 2:

Workgroup Charge

The National Advisory Mental Health Council Workgroup: Setting Priorities for Basic Brain and Behavioral Science Research at NIMH was charged with reviewing the existing NIMH portfolio in molecular, cellular, and behavioral neuroscience, basic behavioral, and basic cognitive science and, considering relevance to mental disorders, recommending priority areas for research funding. In pursuing this charge, the workgroup was asked to address the following questions:

1. To build a basic science foundation that integrates the multiple levels of analysis of the brain with the complex analysis of behavior and the environment:
   - What topics, questions, or domains of research are poised for such integrative approaches?
   - And of these, which are most relevant to elucidating disturbances seen in mental and behavioral disorders?

2. To accelerate the translation of knowledge from the basic sciences to clinical science:
   - Which specific issues, challenges, aspects of disorder and disability can benefit most readily from the translation of basic knowledge and models?
   - Which topics, models and/or putative mechanisms developed in the basic sciences are ripe for testing and validation in real-world clinical settings?
   - Which areas are less likely to have an impact on mental disorders?

3. With the completion of the human genome project:
   - How should the basic sciences portfolio in mental health be developed to facilitate innovation?
   - What is the optimum balance between discovery-based and hypothesis-testing research?