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NATIONAL ADVISORY BOARD ON MEDICAL REHABILITATION RESEARCH

Meeting on

MAY 9-10, 1991

**NATIONAL INSTITUTE OF CHILD HEALTH
AND HUMAN DEVELOPMENT**

NATIONAL CENTER FOR MEDICAL REHABILITATION RESEARCH

WHO ARE WE?

AND

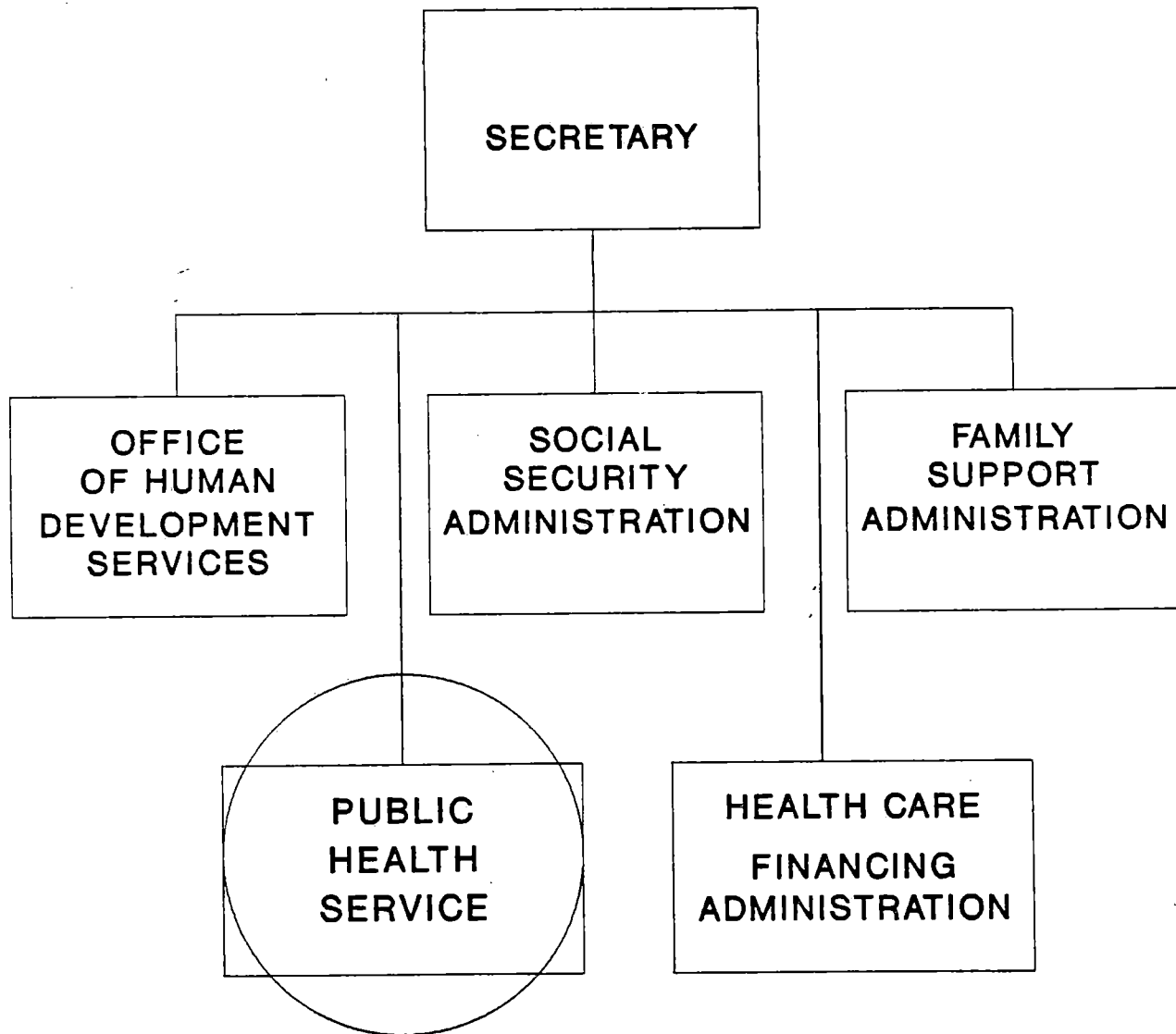
WHAT ARE WE DOING HERE?

DEPARTMENT OF HEALTH AND HUMAN SERVICES

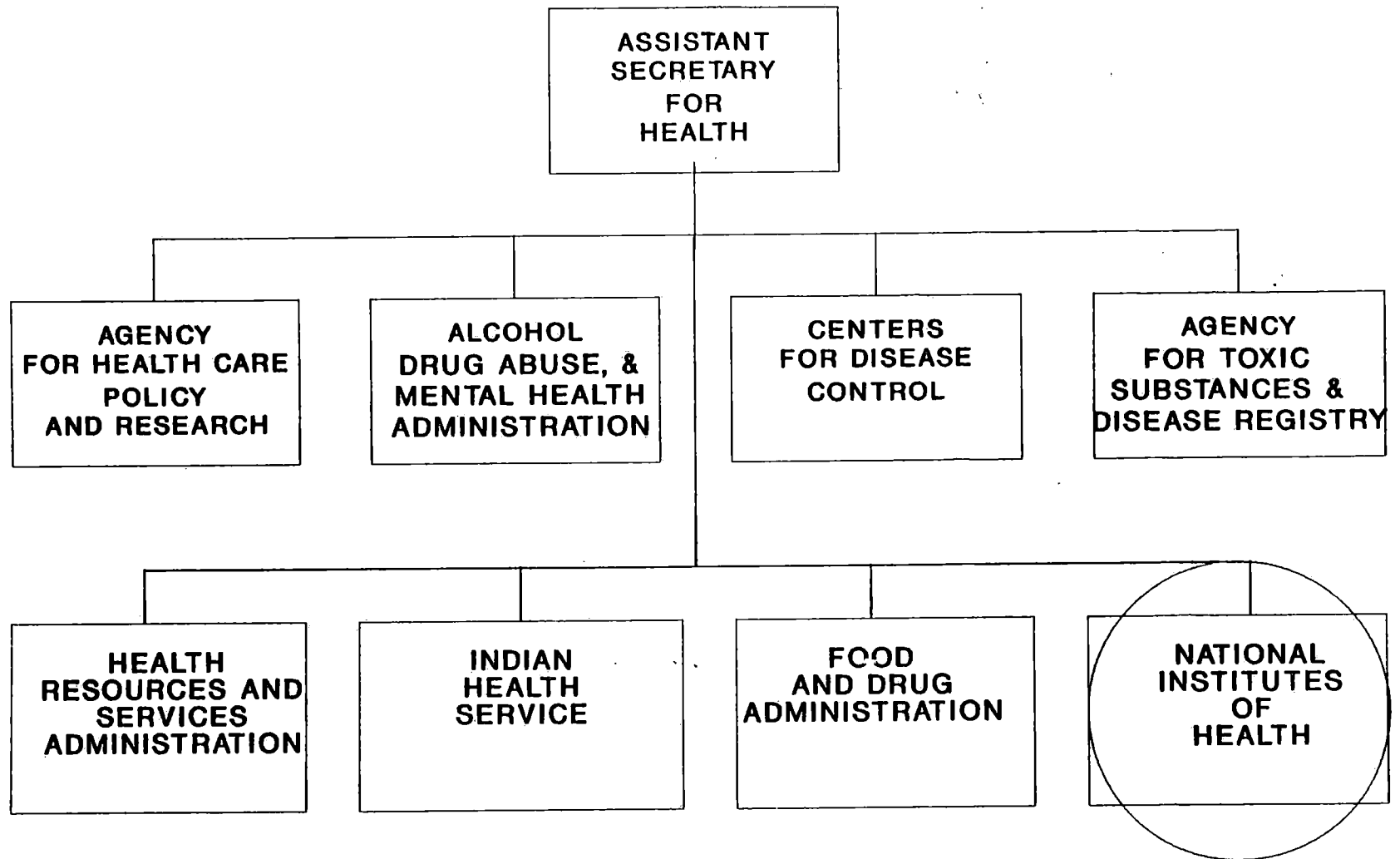
- . . . THE CABINET-LEVEL DEPARTMENT OF
THE EXECUTIVE BRANCH MOST
CONCERNED WITH PEOPLE AND MOST
INVOLVED WITH THE NATION'S HUMAN
CONCERNS.**

- . . . A DEPARTMENT OF PEOPLE SERVING
PEOPLE, FROM NEWBORN INFANTS TO
OUR MOST ELDERLY CITIZENS.**

DEPARTMENT OF HEALTH AND HUMAN SERVICES



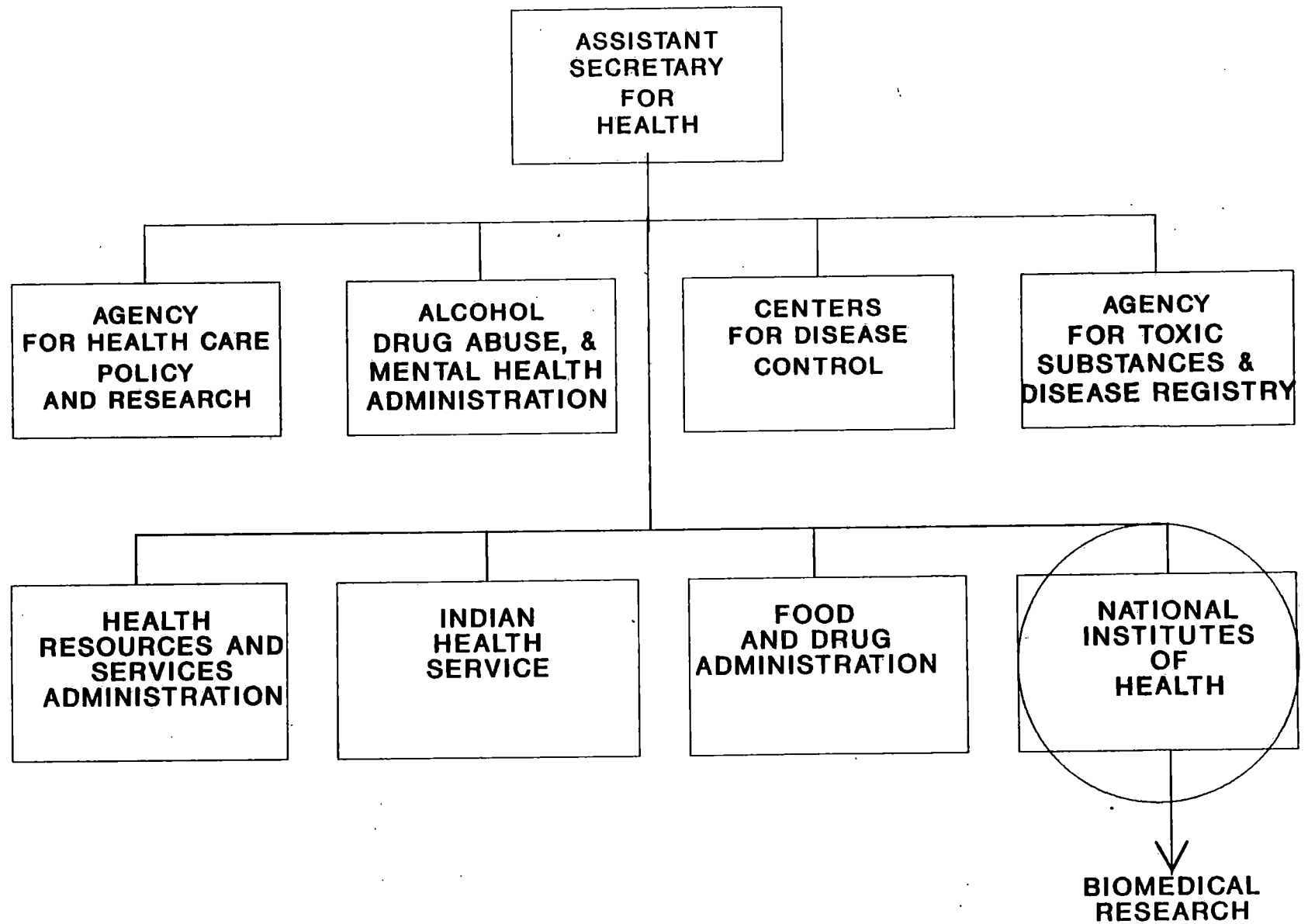
PUBLIC HEALTH SERVICE



HEALTH

- **RESEARCH - TO DEVELOP NEW KNOWLEDGE ABOUT HEALTH**
- **TEACHING - TO TRAIN HEALTH PERSONNEL**
- **SERVICE - TO PROVIDE HEALTH CARE**

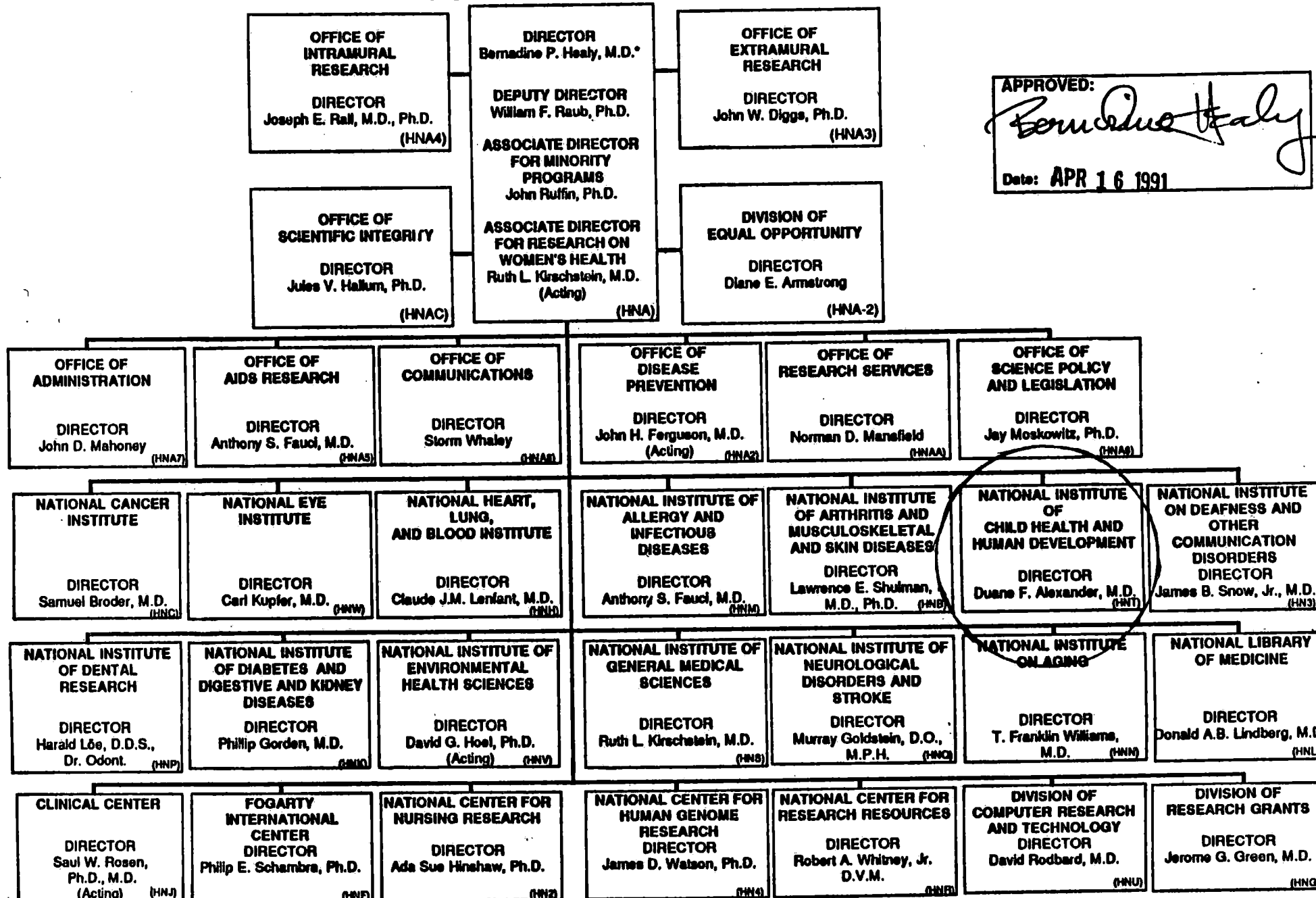
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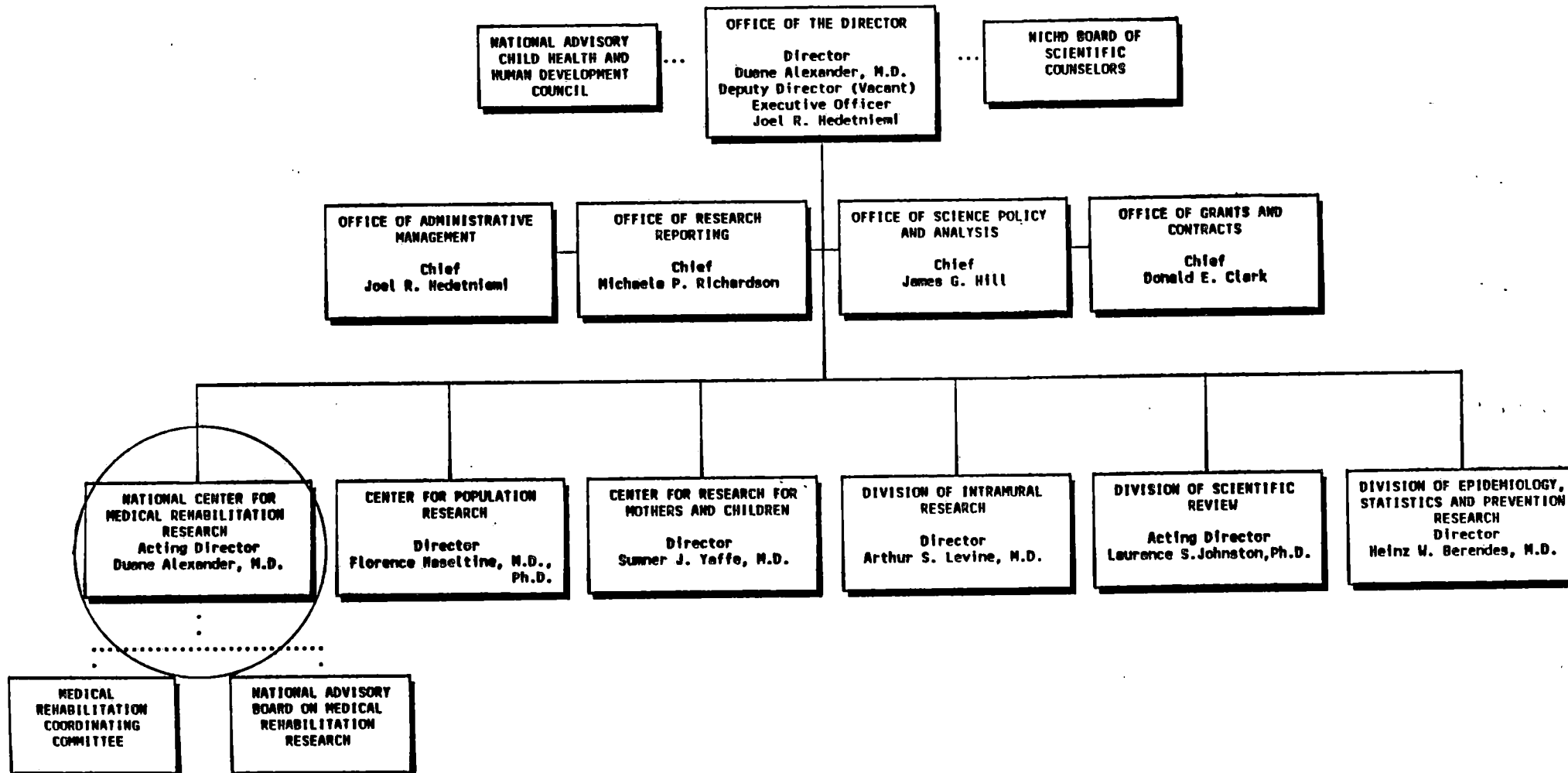
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

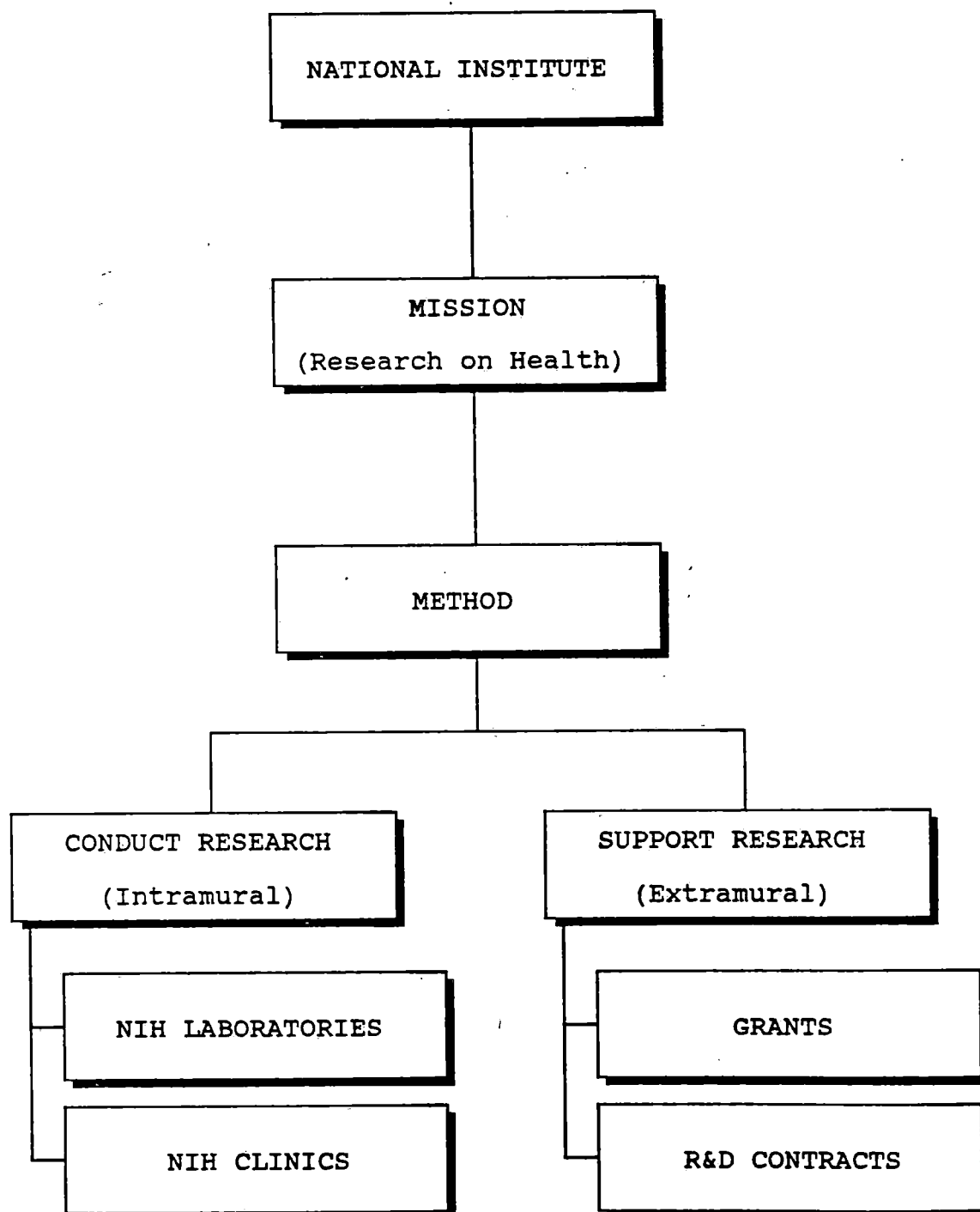
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NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT



NATIONAL INSTITUTES OF HEALTH



**NATIONAL INSTITUTE OF CHILD HEALTH
AND HUMAN DEVELOPMENT**



**NATIONAL CENTER FOR MEDICAL
REHABILITATION RESEARCH**



NEUROPHYSIOLOGICAL DYSFUNCTION

MUSCULOSKELETAL DISORDERS

CANCER REHABILITATION

GERIATRICS

DEVELOPMENTAL ISSUES

ASSESSMENT & EPIDEMIOLOGY

BIOMECHANICS & ENGINEERING

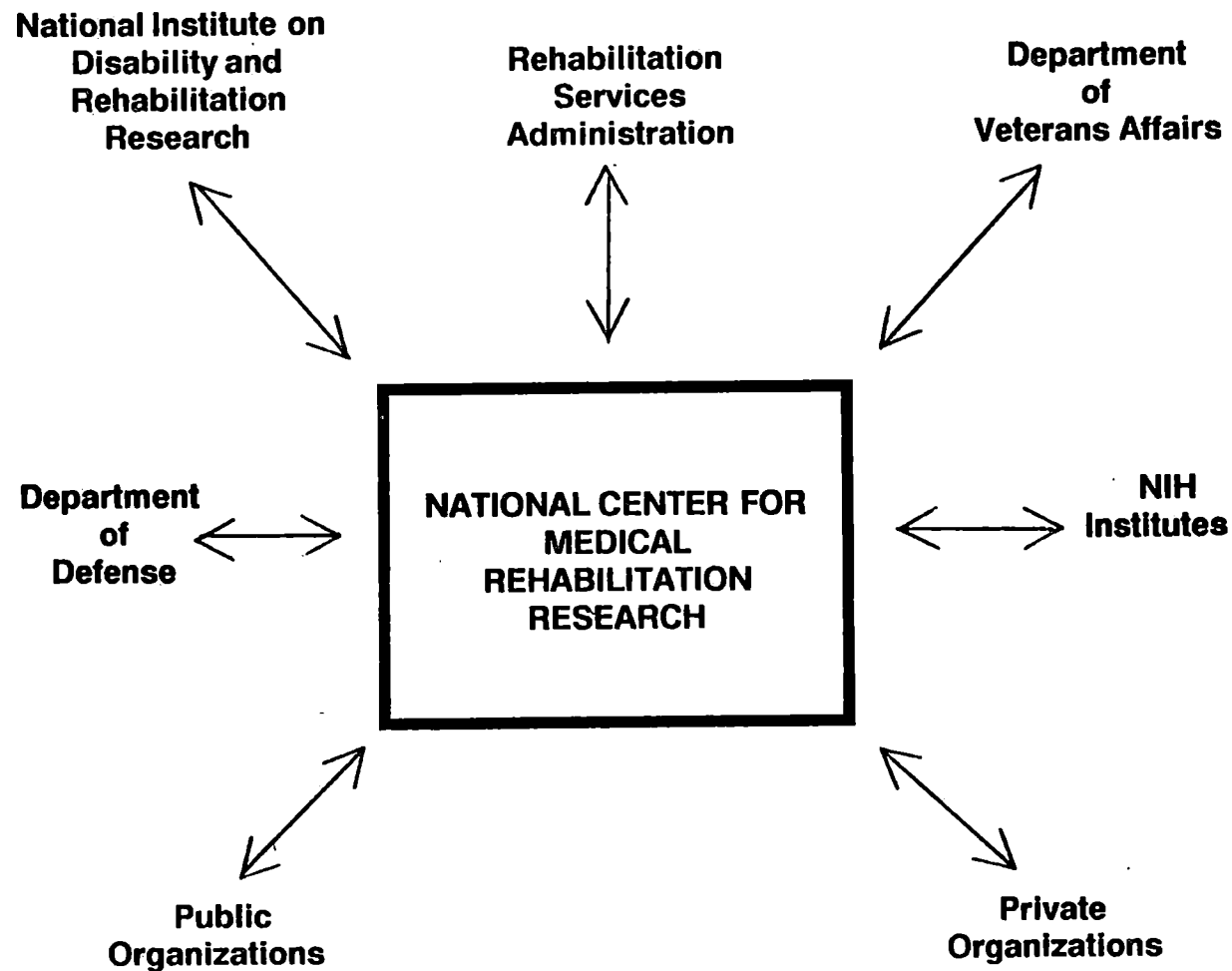


RESEARCH GRANTS

RESEARCH TRAINING

R & D CONTRACTS

COORDINATION



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NATIONAL ADVISORY BOARD ON MEDICAL REHABILITATION RESEARCH

Meeting on

MAY 9-10, 1991

PROGRAM PROJECT (P01)

SUPPORTS A BROADLY BASED, LONG-TERM MULTIDISCIPLINARY RESEARCH PROGRAM THAT HAS A WELL-DEFINED CENTRAL THEME. THE GRANT FUNDS AT LEAST THREE INTERRELATED PROJECTS AND SUPPORTING CORE RESOURCES.

CENTER CORE GRANT (P30)

SUPPORT SHARED RESOURCES AND FACILITIES FOR A LARGE NUMBER OF HIGH-QUALITY, FUNDED RESEARCH PROJECTS RELEVANT TO NICHD'S MISSION. THE CORE SUPPORT ENHANCES QUALITY AND PRODUCTIVITY, PROMOTES COLLABORATION, ENCOURAGES RESEARCH IN THE FIELD AND IMPROVES COST-EFFECTIVENESS. SUBMITTED ONLY IN RESPONSE TO RFA'S.

SPECIALIZED RESEARCH CENTER (P50)

SUPPORTS A LARGE RESEARCH PROGRAM CONSISTING OF AT LEAST THREE RELATED PROJECTS AND SUPPORTING CORE RESOURCES. THE RESEARCH PROGRAMS MAY HAVE MORE THAN ONE THEME, PROVIDED ALL ARE RESPONSIVE TO THE SPECIFIC NICHD CENTER PROGRAM MISSION. SOMEWHAT SIMILAR TO P01, BUT SUBMITTED ONLY IN RESPONSE TO RFA.

INSTITUTIONAL NATIONAL RESEARCH
SERVICE AWARD (T32)

**PROVIDES SUPPORT TO AN
INSTITUTION FOR PREDOCTORAL AND
POSTDOCTORAL RESEARCH
TRAINING.**

CLINICAL INVESTIGATOR AWARD

(K08)

**PROVIDES SUPPORT FOR PROMISING
CLINICALLY TRAINED INDIVIDUALS
WITH A DEMONSTRATED APTITUDE
FOR RESEARCH TO DEVELOP INTO
INDEPENDENT INVESTIGATORS.**

PHYSICIAN SCIENTIST AWARD (K12)

**PROVIDES SUPPORT FOR NEWLY
TRAINED CLINICIANS TO DEVELOP
INDEPENDENT RESEARCH SKILLS AND
LABORATORY EXPERIENCE IN A BASIC
SCIENCE BY PROVIDING INTENSIVE,
SUPERVISED RESEARCH EXPERIENCES.**

CONFERENCE GRANT (R13)

**TO SUPPORT MEETINGS,
CONFERENCES, AND WORKSHOPS.**

RFA-INITIATED RESEARCH PROJECT
GRANT (R01)

**A REQUEST FOR APPLICATIONS IS A
FORMAL STATEMENT THAT INVITES
GRANT APPLICATIONS IN A WELL-
DEFINED SCIENTIFIC AREA TO
ACCOMPLISH SPECIAL PROGRAM
PURPOSES.**

NICHD PEER REVIEW

*PROGRAM PROJECT GRANT

*CENTER CORE GRANT

*SPECIALIZED RESEARCH CENTERS

*INSTITUTIONAL TRAINING AWARD

*CLINICAL INVESTIGATOR AWARD

*PHYSICIAN SCIENTIST AWARD

*CONFERENCE GRANT

*RFA-INITIATED R01 GRANT

*COOPERATIVE AGREEMENTS

*RFP/CONTRACT PROPOSALS

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NATIONAL ADVISORY BOARD ON MEDICAL REHABILITATION RESEARCH

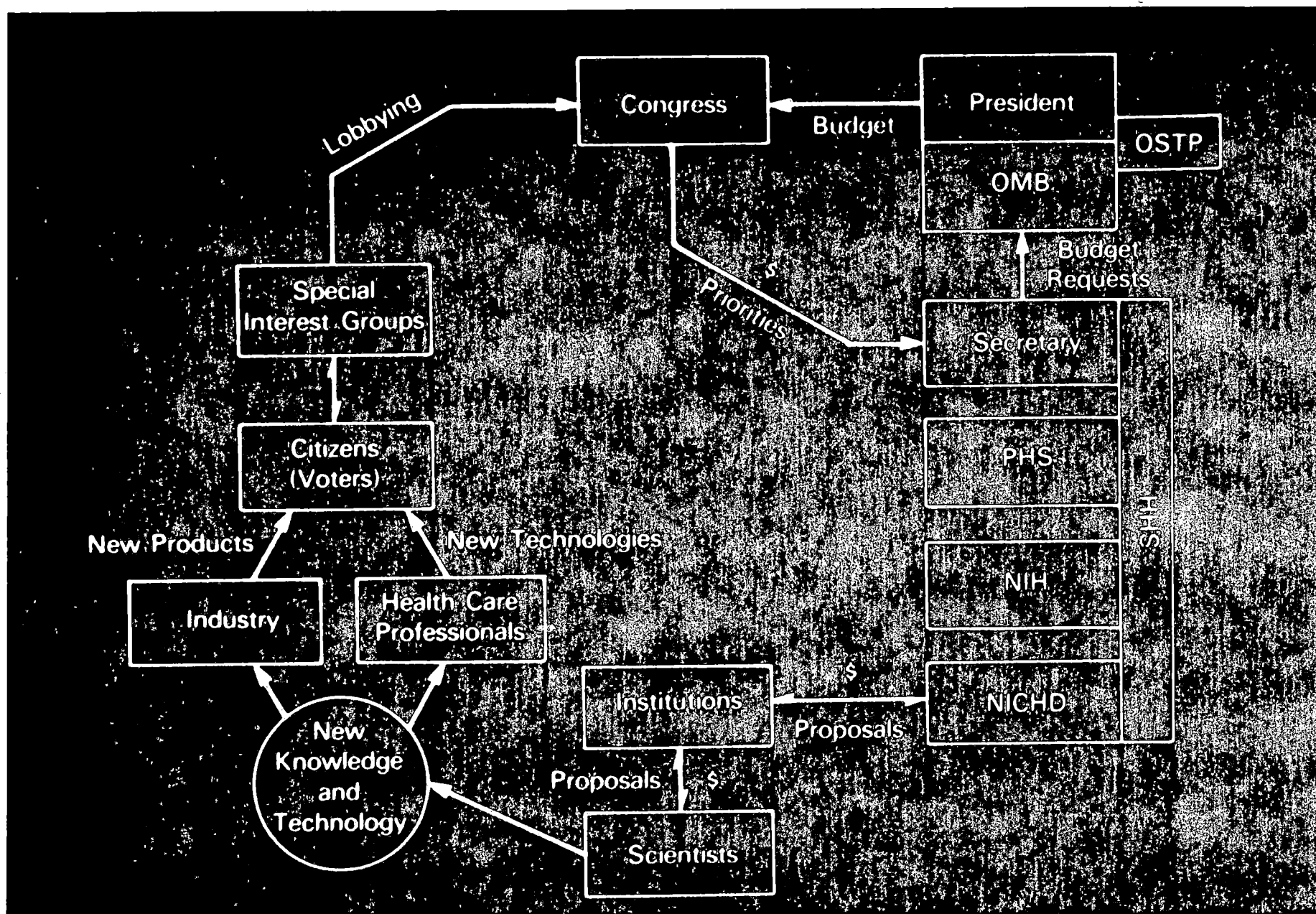
Meeting on

MAY 9-10, 1991

RESEARCH PLANNING AT THE NIH (1963-1991)

- A. 1963** • Budget Stressed
 - Informal Congressional-NIH Strategy
 - Rudiments at NCI (Carrese & Baker)
- B. 1970** • Family Planning and Population Research Act
Five Year Plan for Research and Service
- C. 1971** • National Cancer Program
- D. 1981** • First NICHD Research Plan
- E. 1984** • NICHD Initiates Updates of Plans
- F. 1991** • Development of Research Plan for Medical
Rehabilitation Research





NICHD RESEARCH PLANNING PROCESS

- I. Planning for the Plan**
 - A. Determining the Scope of the Plan**
 - 1. Legislation**
 - 2. Report of the Task Force on Medical Rehabilitation Research**
 - 3. Advisory Board of the NCMRR**
 - 4. NICHD Staff**
 - B. Identification of Liaison Members of the NICHD Council and the NCMRR Board**
 - C. Selection of Study Group (based on scope determined)**
- II. Analysis and Identification of the "State of Science" by the Study Group**
- III. Identification of "Gaps in Knowledge" by the Study Group**
- IV. Development of Recommendations by the Study Group**
- V. NICHD Staff Review of Recommendations**
- VI. NICHD Staff Determination of Action Steps**
- VII. Coordinating Committee Review and Endorsement of Plan**
- VIII. NCMRR Board and NICHD Council Review and Endorsement of Plan**
- IX. Publication of the Plan**
- X. Periodic Update of the Plan**



OUTLINE OF AN NICHD RESEARCH PLAN

- I. Description of the Health Problem(s) and Scope of the Plan**
- II. Description of the Process Used to Develop the Plan**
- III. Scientific Chapters (based on the Scope)**
 - A. The "State of Science"**
 - B. Gaps in Knowledge**
 - C. Recommendations**
 - D. Staff Review**
 - E. Action Steps**



May 15, 1991

TO: Members, National Advisory Board on Medical Rehabilitation Research

FROM: Mr. James G. Hill
Chief, Office of Science Policy and Analysis
National Institute of Child Health and Human Development

As a follow-up to the Board meeting on May 10, attached is a research plan that NICHD staff prepared for our mental retardation and developmental disabilities program.

This model may prove useful as you begin development of a research plan for medical rehabilitation.

**National
Institute of
Child Health
and Human
Development**

An Evaluation and
Assessment of the
State of the Science

**Mental Retardation
and Developmental
Disabilities**

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

**National
Institute of
Child Health
and Human
Development**

**An Evaluation and
Assessment of the
State of the Science**

**Report of the
Study Group on
Mental Retardation
and Developmental
Disabilities**

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

September 1986

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FOREWORD

This volume represents an updating and an expansion of the portion of the NICHD Research Plan entitled Child Health and Human Development: An Evaluation and Assessment of the State of Science (published in 1981) that addresses research issues in the area of mental retardation.

Interest in mental retardation and developmental disabilities research is shared by a broad spectrum of scientific disciplines, consumer advocate groups, professional organizations, and government agencies. In recognition of this broad base of concern, the Mental Retardation and Developmental Disabilities Branch (MRDD) felt it appropriate to seek input from all parts of that spectrum in its planning efforts. As noted in the Acknowledgments, expert committees, consumer advocate groups, professional associations, and federal agencies contributed to the planning effort. The chair of each expert committee was chosen by the MRDD Branch, who, in turn, chose committee members. The committees were asked to develop and draft reports that identified the science base undergirding the MRDD Branch's research mandate and suggest future research efforts.

Committee deliberations and planning, in most instances, were conducted as members attended major scientific meetings of their disciplines, and at regularly scheduled meetings of the Mental Retardation Research Center and University Affiliated Facility Directors. The initial report drafts were circulated among committees for review and comment. They were then made available for review and comment to the concerned consumer advocate groups, professional associations, and government agencies. Individuals with an interest in the planning also were provided copies of the committee reports upon request and were invited to provide comment.

Many of the committee reports proved extremely useful in development of the sections that follow. To minimize overlap among sections, some of which inevitably remains, points made in the various reports do not always appear together in a specific chapter. However, since the research directions and opportunities contained in them exceed current budgetary capacity for implementation, staff review was necessary to impose a time frame and make judgments about the centrality of the issues to the MRDD Branch's specific mandate. Some of the committee recommendations indicate need for immediate action. In many of these instances, staff have already moved to implement them. Others delineate research directions and opportunities for productive research extending well into the future. At the end of each section of this document is a set of "Action Steps." These represent the Institute's best judgment on actions that will take place in the future taking into account the Institute's mission and the likely availability of resources.

It is important to note here that the benefit of the guidance provided in the committee reports will not be restricted to the MRDD Branch, or to the NICHD. As is to be expected, given the multifaceted nature of mental retardation and the distribution of federal research responsibilities reviewed briefly above, much of the material has implications for other Branches of the NICHD, for other federal agencies, and even for state governments. MRDD staff will share the information accordingly and work toward maximum coordination and minimum duplication of effort.

EXECUTIVE SUMMARY

The National Institute of Child Health and Human Development (NICHD) has primary responsibility, within the National Institutes of Health (NIH), for research concerning maternal and child health. As part of this broad mandate, the NICHD supports research into the problems of mental retardation and related aspects of human development. Mental retardation is a lifelong problem, with multiple causes that require study of the full range of developmental variables. It is a major health and social issue affecting millions of Americans and leading to annual public expenditures (federal, state, and local) of billions of dollars.

The Institute's Mental Retardation and Developmental Disabilities Branch (MRDD) is the main locus of the NICHD's support of research into this complex and costly set of problems. To strengthen its research effort and to minimize duplication, the MRDD Branch maintains close liaison with other branches within the NICHD and with other federal agencies supporting research relevant to mental retardation.

More than half the research supported by the MRDD Branch of the NICHD is conducted in 12 Mental Retardation Research Centers (MRRCs) across the country. Ten of the 12 centers are administratively and functionally joined with a University Affiliated Facility (UAF) supported through the Division of Maternal and Child Health and the Administration on Developmental Disabilities. The UAFs provide clinical training for the professions involved in treating mentally retarded individuals.

Contributions from a broad spectrum of scientific disciplines and subject areas are essential for the elucidation, prevention, treatment and amelioration of mental retardation and developmental disabilities. This summary of the Mental Retardation and Developmental Disabilities Plan is organized accordingly.

Epidemiology

Epidemiology is the study of the distribution and determinants of disease and other health problems as they occur in populations. Much valuable research has been done on the causes and concomitants of mental retardation and developmental disabilities, but little has been translatable so far into terms applicable to general populations.

There are three categories of epidemiologic studies: descriptive, analytic, and experimental (clinical trials). Each method is appropriate in certain circumstances. But each method can also produce biased results if not performed correctly and, should not be applied to the general population.

Lack of data presently inhibits adequate pursuit of much important epidemiologic work on mental retardation and developmental disabilities. Needed data include vital statistics data bases, institutional and program records data bases, and specialized longitudinal data collection efforts.

Staff Review

Research training to prepare epidemiologists for research in the field of MRDD has lagged. Earlier, the Branch supported one training grant on the

epidemiology of MRDD. It has since been eliminated in the strong competition for training grant funds. A replacement program is needed. Data bases to support epidemiological work on MRDD are sorely lacking. Among other planned activities to improve the data available for study of MRDD, the Branch will give serious attention to epidemiologic data needs.

Action Steps

- o Convene a national conference on data bases to support reliable epidemiologic studies of MRDD
- o Hold a conference on behavioral teratology which involves epidemiologists
- o Issue a program announcement calling for submission of institutional training grants including epidemiological work concerned with MRDD
- o Initiate an epidemiological study to determine the incidence and prevalence of mental retardation in the United States

Developmental Factors

Prematurity/low birth weight is associated with an elevated relative risk for a number of problems including mental retardation and developmental disabilities. Rapid development of intensive obstetric and neonatal care and the increasing survival of smaller babies has made the problems of the very low birth weight baby (VLBW - less than 1500 gm) more prevalent. While constituting only about 1 percent of live births, VLBW babies contribute a large proportion of infant deaths, and have the highest relative risk for handicaps in survivors.

Because prematurity/low birth weight is related to so many medical, behavioral, social and personal problems, a priority should be placed on studies which have promise in delineating etiologic factors and can thereby contribute to prevention. The relationships between low birth weight and such variables as parental socioeconomic status, maternal age, and birth order have been repeatedly demonstrated. But the biologic significance of such variables is poorly understood and deserves high priority.

Developmental Neurobiology. Development of the nervous system is of obvious importance in the search for causes and treatment of mental retardation and associated developmental disabilities. Recent years have seen a tremendous increase in our knowledge, much of the progress involves movement from phenomenological studies to the cellular and molecular basis of development. Major areas that now merit priority attention include the pathway of differentiation followed by cells, axon outgrowth and target recognition, neuronal cell death, hormonal influences on neuronal development, and the influences on neuronal differentiation and survival of the sensory environment of the organism. The new techniques of imaging and the availability of excellent animal models should be exploited.

Staff Review

In conjunction with studies of developmental neurobiology, particular attention should be paid to Rett Syndrome, a baffling and progressive neurological dysfunction. This condition has been described in all races

and all parts of the world and so far seems restricted to girls. The Rett Syndrome represents a biologically based behavioral phenotype and provides an excellent opportunity to learn more about the neurological basis of behavioral disturbances.

Action Steps

- o Issue an RFA for studies of the factors that control nerve growth and interactions.
- o Issue a program announcement on the development of experimental models with emphasis on animal models of inherited neurological disease.
- o Issue an RFA on Rett Syndrome.

Genetics, Cytogenetics, and Inborn Errors of Metabolism. Much progress has been made in identifying the genetic basis of mental retardation and related disorders. About 40-60 percent of currently known causes of moderate to severe mental retardation have a genetic component. There have also been exciting recent advances in molecular genetics and gene mapping which hold promise for more sophisticated and wider ranging antenatal diagnosis, more and better genetic markers to identify carriers of defective genes, and eventual treatment of the underlying defect through direct gene therapy.

Gene identification should be given high priority, as well as new techniques of antenatal diagnosis (especially chorion villi sampling), and basic research into the potential for somatic cell gene therapy. There is also a continuing need for research into the hereditary patterns, natural history, variation in expression, and medical management of the many genetic and partly genetic disorders associated with mental retardation. Priority areas include X-linked mental retardation, Down syndrome, the problems of PKU offspring, lysosomal storage diseases, the riddles of partial expression (particularly in the neurocutaneous disorders), experimental therapies in enzyme replacement, reproduction in the mentally retarded, and natural history of genetic diseases associated with MRDD.

Staff Review

Research advances in this area are rapid. For this reason, the Branch has not waited for completion of its planning effort to implement a cooperative study to evaluate the safety and efficacy of chorion villi sampling (CVS) as a technique for prenatal diagnosis. This study is now in progress.

It should be noted that large numbers of mentally retarded children, mostly with Down syndrome, have traveled to West Germany for "cell therapy." Staff review of this treatment has found little scientific justification. In addition, there is now the danger that the injected cells, drawn from animal fetal tissues, may carry a slow acting virus. Because large numbers of children have received and will receive this treatment, watchful surveillance has been advised.

Action Steps

- o Convene a workshop on the molecular biology of mental retardation.

- o Issue an RFA on gene therapy using in vitro systems and animal models.
- o Issue an RFP on the development of less invasive prenatal diagnostic methods early in pregnancy.
- o Convene a workshop on the biochemical control of differentiation.
- o Issue an RFA calling for applications concerned with experimental enzyme replacement therapies.
- o Maintain surveillance of cell therapy for the possibility of slow virus infection.

Nutrition, Teratology, and Developmental Pharmacology. Many MRDD-related disorders result from nutritional inadequacies and exposure to toxic substances, either preconception, in utero, or postnatally. The fields of nutrition, teratology, and developmental pharmacology have increasingly overlapping roles to play in identifying the etiology and ways of preventing or ameliorating such disease.

There is a major research need to develop markers that can be used clinically in newborn and developing infants to identify risk factors, pre- and postnatal. In addition, the new techniques of molecular biology need to be applied to mammalian embryology. Specific areas needing research include early human gestation (in particular the process of spontaneous abortion), paternal effects on development, effects from toxic exposure, effects of drugs on intrauterine and extrauterine growth, the spectrum of fetal alcohol effects and their associated risk factors, the delayed effects of abnormal early development, and the potential for in utero therapy.

Staff Review

Considerable research already has been conducted on the effects of undernutrition on the developing brain and on the long-term effect of undernutrition in early childhood on later growth, intelligence, and behavior. Increased attention is now rightly being given to the effects of mild protein deficiency during pregnancy and its potential long-range effects across generations. On the basis of existing evidence, it has been hypothesized that "familial" mental retardation and other learning disorders of unknown etiology have nongenetic intergenerational effects as important causal factors.

Relative to biologic measurement techniques, behavioral measurements--particularly those concerned with higher order mental functions (intelligence) and social behavior--appear less refined. Strengthening and expanding the tools and methods used in behavioral teratology for study of these issues is needed.

Branch interest is shared by others inside and outside the NICHD. Branch staff maintain a cooperative liaison with the Genetics and Teratology Branch of NICHD and with relevant outside agencies in order to assure support and progress in these fields.

Action Steps

- o Issue an RFA calling for studies employing interdisciplinary research on intergenerational effects.
- o Support a program project to investigate intergenerational effects using an appropriate animal model.

Obstetrics and Perinatology. There have been major advances in obstetrics and perinatology in the last 15 years with a concomitant increase in infant survival and decrease in neurological residua. Paradoxically, these very advances have made it increasingly clear that we know little about the factors causing the remaining damage. In particular, we have much to learn before we can disentangle the effects of intrauterine and perinatal factors (such as infections and asphyxia) from those of developmental anomalies and metabolic problems.

Priority areas for research include prospective studies of trends in the prevalence of neurodevelopmental disorders, correlated with changes in obstetric and neonatal practices and attitudes. There is also a need for prospective controlled clinical studies using birth route as an independent variable to test hypotheses about pressure on the vertex during birth. The newer imaging techniques should be evaluated for their ability to detect forms of fetal distress that are neurologically threatening. The effects of maternal work on environment and outcome are also important. Finally, the mechanism by which neonatal seizures cause further damage, and the effects of cerebral edema and cerebral vascular control are crucial areas for research.

Staff Review

Preterm births and low birth weight infants are a major concern for the MRDD Branch. These biologically vulnerable infants are the subjects of intensive study under the rubric of early identification and early intervention programming. The methods and outcomes of care provided these infants in neonatal intensive care units (NICU) is also a matter of strong research interest. There are important issues involving the status of the family that need to be addressed to complement the biological research accomplished in obstetrics and perinatology.

Action Steps

- o Encourage applications concerned with the effects of life styles on pregnancy outcomes.
- o Work with the Pregnancy and Perinatology Branch of the NICHD to develop research applications on prenatal and perinatal factors related to brain disorders with particular reference to mental retardation.

Behavior

The behavioral aspects of mental retardation and developmental disabilities are central to the mission of the MRDD Branch of the NICHD. The fundamental principle underlying study of these aspects is that behavior of organisms and the environmental conditions in which this behavior occurs influence each other in a continual process.

Psychobiological Processes. The several disciplines encompassed by psychobiology have made substantial contributions to the elucidation of mental retardation and developmental disabilities through multidisciplinary approaches that bridge the gap between the biological and behavioral sciences. Behavioral and psychophysiological techniques for segmenting information flow through the nervous system have produced particularly impressive gains in analyzing sensory-perceptual processes. What is needed now is interdisciplinary research employing longitudinal designs combining animal models and sophisticated new techniques of behavioral and psychophysiological measurement of children. The central focus should be that large proportion of the MRDD population who exhibit mild retardation, the etiology of which, for the most part, remains unknown. This is because the tools of psychobiology are well equipped to measure distinctions at an extremely detailed level. Subject areas for emphasis include: family quantitative studies (including intergenerational effects), development of sensory and motor systems, and the effects of stress on development.

Staff Review

Research evidence is increasingly able to show intergenerational effects of nutrition, drugs, stress, handling and other agents. The mechanisms responsible for these intergenerational effects are not well understood. Debilitating intergenerational effects of this type present one possible source for the cause of MRDD and expanded studies to explore this issue are needed.

Action Steps

- o Issue an RFA calling for studies on intergenerational debilitating effects.
- o Issue a Program Announcement calling for research on development of sensory and motor systems and the effect of stress on this process during prenatal and early postnatal periods.

Psychological Processes. Recent research developments in the area of psychological processes indicate that the most productive strategy is one that addresses the componential nature of intelligent behavior. Progress in understanding the development of intelligence depends on analysis of interactions among knowledge bases, processing strategies, and metacognition. Other major areas where research is needed include the role of perceptual processes, motor development, and the personality and motivation of mentally retarded people. Research should include structured observations of behavior in naturally occurring settings, and include longitudinal observations.

Staff Review

Because psychological processes is a well-established field of research endeavor and with a complement of well-trained investigators, the Branch proposes to continue programming support for these endeavors while reserving specific initiatives to other areas of research judged to be most in need of stimulation and growth.

It should be noted that a conference on motor skills was held in September 1984 to delineate research needs and opportunities in the area and to chart

future research directions. A publication to disseminate the proceedings of the conference is in press.

Action Steps

- o Give programming emphasis to research on development of motor skills.

Behavior Analysis. Behavior analysis proceeds on the premise that all behavior is a function of observable social, physical, and biological conditions and that the behavioral status of retarded individuals is in part the direct result of how the social environment responds to their behavior. The most important conclusion in the field is that even profoundly retarded individuals can achieve significant improvements in learning and performance. High priority should now go to development of objective, reliable measures of the basic determinants of behavior; the study of antecedent events, generalization, and maintenance; the controversial issue of drug therapy as a means of behavior modification; the etiology of specific behavioral disorders; and the integration of behavior analysis with other scientific disciplines.

Staff Review

Behavior analysis represents one of the most powerful tools in the MRDD research armamentarium for improving the quality of life of persons with MRDD. Its power is recognized in its applied consequences and in the elicitation of effective modification of human behaviors. Drug therapy is a prevalent means of behavior modification of the retarded, however, experimental evidence to support the use of many drug therapies is lacking. Study of the effects of drugs on behavior and of learning-based therapies as an alternative to drug treatment must be conducted.

Action Steps

- o Issue program announcements encouraging research on drugs and behavior and for applied behavioral research.

Functioning and Social Adaptation

The functioning and social adaptation of the mentally retarded is a major focus of MRDD Branch efforts. Areas of concern include communicative processes, early diagnosis and intervention, and socioecological processes.

Communicative Processes. The most significant accomplishment in this area in the last 25 years is the realization that language training may be the most effective system for making significant alterations in the development of retarded children. A number of urgent issues remain to be resolved, however. Much work still has to be done describing longitudinally the diversity of language and communication problems among the many subgroups of the MRDD population. In addition, a complete theoretical model for integrating the information from descriptive and application efforts is essential for optimal design of language intervention programs. Third, research must interrelate data from different settings to develop composite pictures of language performance. Finally, assessment and evaluation must make full use of computer and engineering technologies.

Staff Review

Language is a culturally embedded function of social development that is usually learned without explicit instruction. However, for many children with mental retardation and developmental disabilities language is seriously delayed or disordered. Such problems indicate that the usual conditions for language acquisition are absent, inadequate, or dissonant. In such instances there should be explicit efforts to intervene and to produce an arranged set of conditions to facilitate language. Staff judgment on this issue prompts a proposal to conduct a conference on "The Teachability of Language," to address crucial aspects of language intervention for the mentally retarded.

Branch staff finds particular urgency in the need to study at-risk infants for the purposes of a) deriving early measures of language that have predictive validity for educational achievement and b) to determine the relationships between earlier and later language abilities.

Action Steps

- o Convene a conference on the Teachability of Language in FY 1987.
- o Place a longitudinal data base for the language development of retarded children on the agenda for the proposed National Conference on Data Bases (see Section II).

Early Diagnosis and Early Intervention. The proliferation of infant stimulation and intervention programs, and their rich array of procedures for targeting specific interventions for specific problems, attests to the enormous progress in this field over the last two decades. However, there is still a fundamental paradox that future research must confront: little relationship exists between assessments in the first year of life and in later childhood. Research should be emphasized that recognizes that developmental outcomes are the product of the interaction between children with specific strengths and weaknesses and parents with specific attitudes, knowledge, and coping abilities. In addition, we need evidence from early intervention programs that use research designs and analysis models that include explicit causal hypotheses about interactions between characteristics of the child, the family, and the social context.

Staff Review

The MRDD Branch proposes continued strong programming on early identification and early intervention for infants at risk because of its potential for prevention and for the support and assurance these activities afford families during their children's early years.

Action Steps

- o Issue RFP to develop methods for assessment of caretaking environments.
- o Issue RFA on families with handicapped children.
- o Issue RFA for research on effective intervention strategies which facilitate parent interactions promoting competence with emphasis on effective social and cultural variables.

- o Hold a conference on attention, temperament, motivation, exploration and play in mentally retarded children.
- o Issue RFA to study coordination of pediatric services and early intervention programs.
- o Issue RFP to study the effects of motor therapies on motor development and on the facilitation of educational and social interventions.
- o Continue programming of research on developmental follow-up of biologically and environmentally at-risk infants.
- o Monitor contract for development of assessment strategies for identification of biologically at-risk infants.

Socioecological Processes. Social and ecological perspectives bearing on mentally retarded persons is a relatively new area of research. The shift from almost exclusive emphasis on traits of the person to an emphasis on person/environment interactions was slow in coming. Even so, some significant advances in knowledge have been made. It is now realized that mentally retarded persons should be studied in the full range of their natural activities, that simple measures of individual attributes are not predictive of community adaptation, and that cultural differences play a part in any understanding of their lives. We need research that encompasses the life span of mentally retarded persons, focusing cross-sectionally and longitudinally on continuities and discontinuities in life span. More attention is also needed on quality of life and life satisfaction of mentally retarded persons. Finally, research is needed to identify the experiences and interactions (including not only early socialization but cultures into which such people move later in life) that lead to improved social competence.

Staff Review

The social action programs of the past 25 years on behalf of MRDD persons have greatly expanded their opportunities for participation in a fuller range of life activities. In this context, social competence has emerged as a critical variable within the range of MRDD research concerns. Expanded research involving studies of the transactions of persons with MRDD and their expanded environments is needed.

The social adaptation of persons with MRDD to the complexities of community life is not accomplished without stress. Reports to staff from MRDD-oriented pediatricians and internists working with older persons with MRDD indicate growing concern with their general health care after school age and frequency of psychosomatic illnesses (ulcers, hypertension) in this population. Because MRDD research and services have been concentrated on the early developmental years, few studies on the health and problems of social adaptation of older persons with MRDD have been reported (this latter area is one of potential overlap with other agencies.)

Action Steps

- o Issue a program announcement on quality of life among MRDD persons, especially those of minority groups.

- o Hold a conference on the measurement and development of social competence in MRDD individuals.
- o Confer with staffs of other agencies regarding their interest in studies of health and health care of persons with MRDD past school age. Issue an RFP on this issue contingent upon the outcome of the meeting.
- o Hold a conference on adaption to postsecondary education settings such as sheltered workshops, competitive work settings, and group homes.

Family and Community

Epidemiological studies are required to identify subgroups of the population at particularly high risk for forms of mental retardation (for example, fetal alcohol syndrome, lead toxicity) which can only be prevented through information in a family and community context. Once identified, these groups must be studied to determine how their values influence behavior and the sources of these values. Then efforts to change values require study of the relative importance of transactions among the groups (target youth, peers, family members, and other members of the general social support network).

In the last decade policy has favored community residential placement over large institutions, as well as parental rights in choosing educational programs. Research is badly needed to clarify under what conditions community placement (including in-home placement) is advantageous. This research must identify differential adjustment and psychological growth in the various residential alternatives. It must also recognize, in the case of in-home placement, that the stress placed on different family members varies and also changes over time as each person (the mentally retarded person, nonretarded siblings, parents) passes through different stages of life.

The early belief that all retarded people could achieve near normal development with proper interventions generally has been contradicted by historical evidence. It is important to identify those factors (child, family, environment) which are predictive of responsiveness to the interventions versus those which are not. Studies are needed of life-span development using large longitudinal data sets, in-depth cognitive and social assessments over time on smaller samples, and exploratory studies of novel medical and educational interventions.

Finally, there is very little research on the problems of aging parents and their adult mentally retarded offspring. We are all subject to increased stress and disease as we age. There is every reason to suspect that the mentally retarded are even more susceptible. We need answers to several questions, including: When is a specified mildly retarded individual to be considered aging? What effect does the community movement have? How do mentally retarded adults adjust to separation from natural parents or lifetime association with them?

Staff Review

The past 25 years have seen major changes in our nation's approach to the care of MRDD persons. Prominent among these changes is the shift from an

orientation for provision of care in institutional settings to one of mainstreaming persons with MRDD in their families and communities. With these changes there is growing demand for expanded research concerned with the problems of adaptation to life in the community for retarded persons and their families.

With advancing research knowledge, advances in medical care, and the growth in the provision of services and community education, persons with Down Syndrome are living longer, have been moved into home and community care, and are engaging more broadly in the work force. For these reasons, special attention needs to be given to Down Syndrome research in the areas of adolescence, transitions from school to work, family adaptation to persons with Down Syndrome living at home, and aging.

Mainstreaming the more severely impaired from residential care to community based Intermediate Care Facilities is not without problems. Concern has been expressed for the quality of care provided in these facilities, and for mixes of MRDD conditions involving placements of severely impaired, defenseless persons with clients exhibiting disturbed, aggressive behaviors. The foregoing suggests continuing need for research and evaluation across the continuum of care provisions for the MRDD population. These are research needs properly addressed by NICHD and other concerned agencies. Research developments and social action programs also forecast the continual emergence of new ethical issues needing examination. The NIH has recognized this need by appointing an ethicist to the staff of the NIH Clinical Center and by frequently including ethicists in Consensus Development Conference Panels. The sensitivity of MRDD Branch staff to ethical issues is reflected in the decision for NICHD to join with the John F. Kennedy Center at George Peabody College of Vanderbilt University in sponsoring the May, 1985 conference at the Center entitled "When Are Intervention Decisions for Severely Retarded People Ethical? Toward an Ethically Relevant Research Agenda."

Action Steps

- o Issue an RFA to stimulate research on families with mentally retarded members.
- o Issue an RFA on the transition between adolescence and adulthood following consultation with the staff of the Administration on Developmental Disabilities.
- o Hold a conference on the problems of the aging retarded following consultation with staff of the National Institute on Aging, NIH.
- o Bring the research issues highlighted in this section of the Plan to the attention of the Interagency Committee on Developmental Disabilities.
- o Identify ethical concerns on applications supported by the MRDD Branch, analyze their relation to the research planned, and work for satisfactory resolution.

ACKNOWLEDGEMENTS

The dedicated effort given by consultant committees, consumer advocate groups, and government officials to make this report possible is deeply appreciated. In particular, MRDD Branch staff gratefully acknowledge the contributions of the committee chairpersons who gave so freely of their time and effort:

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I. INTRODUCTION

The National Institute of Child Health and Human Development (NICHD) has primary responsibility, within the National Institutes of Health (NIH), for research concerning maternal and child health. As part of this broad mandate, the NICHD supports research into the problems of mental retardation and related aspects of human development. The Institute's Mental Retardation and Developmental Disabilities Branch (MRDD) is the main locus of this support.

Mental retardation is a lifelong problem, with multiple causes that require study of the full range of developmental variables. As such, it exemplifies the multidisciplinary mission of the NICHD. Mental retardation also affects millions of Americans and leads to annual public expenditures (federal, state, and local) of billions of dollars. It is thus a major health and social issue. This chapter begins with a brief review of the scope and significance of the problem and then describes the research strategy of the MRDD Branch.

Mental Retardation: Scope and Significance of the Problem

The causes of mental retardation are biological, psychological, and social acting singly or in combination. Genetic factors and prematurity or other disturbances during pregnancy are among its biological determinants. Infection or injury at birth or in early childhood may also underlie mental retardation. In addition, lack of stimulation, inadequate educational opportunities, and generally deprived living conditions may be causal or contributory factors. The moderate and more severe conditions of retardation can usually be traced to faulty genes, infections, accidents, diseases, and disorders that cause brain damage. Knowledge is needed from almost every branch of science in order to understand the interaction of these elements in the development and behavior of children and adults. Research on the causes, prevention, and amelioration of mental retardation contributes to the understanding of other developmental disabilities as well, including autism, epilepsy, and cerebral palsy, all of which are frequently associated with mental retardation.

Mental retardation is identified clinically by the presence of several signs that include, but are not limited to, a significant impairment of intelligence and a concurrent deficit in adaptive behavior. Typically, these impairments occur before age 18. The identification of mental retardation through the years has reflected varying degrees of emphasis on the two factors. Before the mental testing movement, the primary behavioral characteristic of those referred to as mentally retarded was inadequate social adaptation. With the rise of mental testing, specifically intelligence testing, greater reliance was placed on measured intelligence as the primary characteristic in defining mental retardation. The term intelligence was used to refer to the ability of the individual to master verbal, visual, and mathematical symbol systems, and the concept of intelligence itself became defined by the instruments that purported to measure it.

Because of the ambiguity of definitions, different estimates have been made of the prevalence of mental retardation. The traditional method, based upon the normal distribution of intelligence test scores, places the number of mentally retarded in 1984 at an estimated 7.5 million Americans, or 3 percent of the general population. Some authorities, employing clinical criteria, estimate the frequency at 1 to 2 percent of the population, or between 2.2 and 4.4

million persons. Still other authorities expand the estimated number of retarded individuals by including the less severely affected--that is, persons with IQs up to 80 who have problems in social adaptation. The most difficult cases to classify are individuals who may exhibit subnormal intellectual functioning but who are socially adept, or who score below normal IQ but are able, because of specific formal or informal training, to function successfully at a reduced level in the mainstream of society.

Programs for the mentally retarded vary with the cause, type, and degree of retardation. They involve, either directly or indirectly, many agencies of government at the federal, state, and community levels. Total federal expenditures for support of mental retardation and developmental disabilities programs in FY 1985 amounted to nearly \$8 billion. State and local governments were expected to expend four times that amount. Thus, federal and state outlays are estimated to total well over \$30 billion a year. Such funds are used for a wide range of programs, including prevention, provision for basic needs, residential and community care, health, education and habilitation, and employment.

In 1970, approximately 270,000 mentally retarded persons were cared for in public residential care institutions. By 1980, this figure was reduced to about 139,000 under the impetus of a national program of deinstitutionalization which shifted much of the institutionalized population to community care facilities. Care of these persons costs an estimated \$3 billion per year. Current estimates place 62,397 mentally retarded persons in this kind of care, for which community residential facilities reimbursements--a portion of the total care costs--approximate \$1 billion a year.

The foregoing provides an incomplete picture. The numbers of retarded children and those at risk for becoming retarded are probably underreported. In addition, many retarded persons merge with the population at large upon leaving structured school programs, even though the deficits of the developmental years often continue to reduce their employability, impair their social adjustment, and effect a dependency requiring economic and social support.

The Mental Retardation and Developmental Disabilities (MRDD) Branch

The MRDD Branch supports research and research training related to the biological, behavioral, and social processes that contribute to or influence the development of retarding disorders. To accomplish its mission, the Branch uses the research project grant, the program project grant, center grants, various research training mechanisms, and contract support for development of vital research resources. It also disseminates relevant information to the scientific and medical community as well as to the public at large.

To strengthen its research effort and to minimize duplication, the MRDD Branch maintains close liaisons with other Branches within the NICHD and other federal agencies supporting research relevant to mental retardation. Within the extramural and intramural programs of the NICHD, for example, other Branches have made significant contributions to knowledge about mental retardation--with investigations into the damaging effects of aberrant pregnancies (Pregnancy and Perinatology Branch), difficulties during birth (Pregnancy and Perinatology Branch), adverse factors in early infancy (Pregnancy and Perinatology Branch), the effects of nutritional deficiencies

and imbalances (Endocrinology, Nutrition and Growth Branch), and basic investigations into the genetic and neurophysiological bases of mental deficiency (Genetics and Teratology Branch).

Outside the NICHD, the other federal agencies in the Public Health Service contributing most to the research knowledge base relevant to mental retardation are the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Mental Health (NIMH), and the Division of Maternal and Child Health of the Health Resources and Services Administration (HRSA). The contributions made by the NINCDS are primarily in the area of developmental neurobiology. Those of the NIAID are in the area of infectious diseases. The NIMH has research responsibility for the emotional and psychiatric aspects of mental retardation. The HRSA supports health-related mental retardation research of an applied type. Outside the Public Health Service, major sources of research support are the Department of Education, the National Institute for Handicapped Research (NIHR) in the Office of Special Education and Rehabilitation Services, and the Administration on Developmental Disabilities in the Office of Human Development Services.

More than half the research supported by the MRDD Branch of the NICHD is conducted in 12 Mental Retardation Research Centers (MRRCs) across the country. The primary objective of the MRRC program is to provide facilities for a cohesive, interdisciplinary program of research and research training in mental retardation and related aspects of human development.

Nine of the 12 centers are administratively and functionally joined with a University Affiliated Program (UAP) supported through the Division of Maternal and Child Health and the Administration on Developmental Disabilities. The UAPs were authorized to provide clinical training for the professions involved in treating mentally retarded individuals. They also provide a means for translating the new methods of treatment and care developed through research into services.

The MRDD Branch gives special attention to elucidating the cause of Down syndrome, the most common genetically determined condition associated with mental retardation. Also given high priority are studies of high-risk infants, babies born under conditions associated with susceptibility to later developmental retardation. Family variables and parent (caregiver) -infant interactions strongly influence the development of high-risk infants. Other influences include preschool, school, and the larger community. These factors often determine whether, as the child matures, he or she either drops from risk status or requires continued support to minimize residual deficits. Research that seeks to understand these processes and to find means to increase their positive effects on development is emphasized. In addition to these areas of special interest, research is supported on the more than 250 mental retardation syndromes that have been identified, and the new ones discovered each year. Each requires fundamental research into the underlying processes as well as studies designed to meet the unique needs of the afflicted children. Thus, the Branch supports a comprehensive program of research concerning the etiology and pathophysiology, epidemiology, diagnosis and evaluation, prevention, and amelioration of mental retardation.

II. EPIDEMIOLOGY

Epidemiology is the basic science of public health and has been defined as the study of the distribution and determinants of disease and other health problems as they occur in populations. The fundamental contribution of properly designed epidemiological studies is to produce results that are generalizable to defined total populations.

Much valuable research has been done on the causes and concomitants of mental retardation and developmental disabilities. However, unless the information is translatable into terms applicable to general populations--not just to a specific set of patients who may have very particular characteristics--the conclusions may be distorting or even false when applied to more widely defined groups. This section discusses the crucial principles that should be adhered to when conducting epidemiologically valid research. Then it discusses how these relate to specific priority issues for research in the MRDD area.

The Principles of Epidemiology

There are three categories of epidemiologic studies:

- o Descriptive - the study of the occurrence of a problem in populations with respect to person, place and time.
- o Analytic - studies which search for determinants of a problem. Case-control studies begin with affected persons and attempt to determine background exposures and other characteristics of diseased persons (cases) which are in excess compared to nondiseased persons (controls). Cohort or follow-up studies compare disease rates in persons who are exposed to a hypothetical agent or condition with rates in unexposed persons.
- o Experimental or clinical trials - studies which ascertain whether protection from an exposure or a prophylaxis prevents a disease; or a treatment heals, improves, or cures a disease. Ideally, these trials should be randomized into treated and untreated groups, and both subjects and observers should be blind to the presence or absence of intervention.

Each method is appropriate in certain circumstances. Descriptive studies, for example, can make very real contributions to knowledge about poorly understood conditions, as a first step in defining a problem, its incidence and/or prevalence, the secular trend, and some high risk groups. Each description can lead to rational, testable hypotheses using analytic studies or clinical trials. Unfortunately, each method can also produce biased results if not performed correctly. Many descriptive and analytic studies, for example, are done in teaching and referral hospitals and other centers, whose patients are not representative of the general population.

In this regard, it is well to point out that the NINCDS National Collaborative Perinatal Project studying about 50,000 pregnancies was not representative of the total American population when it was done two decades ago and is not representative now. For instance, excluded from some or all of the twelve

collaborating hospitals were certain high risk groups: unmarried women; women who had no prenatal care; women who were not going to keep their babies. Omission of such high risk groups produces results in both the biomedical and behavioral spheres which may prove spurious.

Clinical trials, if inadequately done, may also result in incorrect conclusions. Worse, they may prevent or at least make more difficult the conduct of well-designed studies which can give the answers sought. In the biomedical sphere, for example, the question of prevention in recurrence of neural tube defects by periconceptional vitamin supplementation of the mothers is currently a matter of controversy. Two studies have been performed on this question, both showing a protective effect. However, both were inadequate because there were insufficient clinical and analytic epidemiologic data to warrant a clinical trial. Both were also subject to important methodological criticisms which cannot be answered without a well-designed clinical trial based on adequate data. Such a trial is now in jeopardy because of the results already obtained, the serious nature of the malformations in question, and the publicity given the studies.

Lack of adequate data inhibits the adequate pursuit of much important epidemiologic data. Needed data include vital statistics data bases, institutional and program records data bases, and specialized longitudinal data collection efforts.

Vital statistics data can serve an important function in both descriptive and analytic epidemiological investigations. For instance, there is great concern about the possible effect of a number of exposures on pregnancy outcome. The number of substances which can possibly be investigated is, for practical purposes, limitless. If parental occupation were on the birth and fetal death certificates, analysis of vital statistics data could possibly lead to hypotheses about problem exposures, and more intensive analytic studies could then be done to test such hypotheses. Parental education is an important variable related to pregnancy outcome and child development, yet there are still three states, California, Texas and Washington, which do not include it on the birth and fetal death certificates. These states constitute one-fifth of all U.S. births, and have high representation of Asian and Mexican-American births. In some states there has been an effort to improve the quality of data on the birth, fetal death, and death certificates, and to link infant death certificates to birth certificates. However, fetal deaths typically are still poorly recorded and analyzed by the states and the National Center for Health Statistics. Better descriptive data relative to fetal deaths would help to define the magnitude of various etiologic factors, which may also be important in abnormal live births as well. A major deterrent in developing more accurate and pertinent vital statistics data is the fact that many physicians, nurses, and hospitals fill out the birth and fetal death certificates in a haphazard way, or, in some cases, refuse to report anything but the minimal data to register the birth.

Institutional and program records data bases, which are potentially extremely fruitful but rarely available, include records from state institutions, Crippled Children's Services, Medicaid, hospital discharge records, and school district special education programs. There is, of course, an interest on the part of everyone involved in maintaining confidentiality with respect to such

data, and, therefore, some resistance to their use. A number of studies utilizing such data bases have already been accomplished with strict adherence to confidentiality, however, indicating the feasibility of such studies. A few states even have been successful in linking vital statistics records to other data bases.

Finally, some important questions can only be answered by special longitudinal data collection efforts; major reasons why these data are not more frequently collected are the expense and time involved. This inhibits investigator interest in conducting such studies and funding agencies to support them (for more detail see section XIII).

It has become increasingly clear that considerable heterogeneity characterizes many problems in the MRDD area. That mental retardation has a multiplicity of different causes, genetic and nongenetic, is well known. It is less well known, for example, that different types of cerebral palsy exhibit different epidemiologic patterns. Or that there are more than 150 distinct syndromes involving oral clefts, and that even isolated clefts may be heterogeneous in origin. Even the neural tube defects, usually thought of as being rather homogeneous, exhibit heterogeneity, based on both clinical and epidemiologic evidence. More sophisticated studies need to be designed in the future in order to deal with the question of heterogeneity, based on the best available clinical diagnosis and epidemiologic principles.

Many clinical investigators are not adequately familiar with epidemiologic principles and methodology. It is also true that many epidemiologists are not sufficiently familiar with the clinical and other aspects of the problems they are investigating. Both perspectives are essential in mental retardation and developmental disability research, indicating the desirability of more collaboration between the two groups.

High Priority Research Issues in the Epidemiology of Mental Retardation and Developmental Disabilities

Down Syndrome. Down Syndrome (DS) is one of the most prevalent and important causes of mental retardation. It has long been known that about 95 percent of the cases are related to Trisomy 21, an extra complete chromosome 21. In spite of the dramatic relationship to maternal age, it now seems clear that in about 15 - 20 percent of these cases, the extra chromosome in Trisomy 21 is paternally derived. Because this probably represents too much "noise" in any study which depends only on clinical diagnosis or standard karyotyping, it seems necessary to repeat the epidemiology of DS based on parental origin of the extra chromosome in Trisomy 21. Understanding the relationship of the occurrence of DS to maternal and paternal factors should serve as the basis for studies directed toward uncovering the etiologic factors in Trisomy 21.

Because DS can be diagnosed at birth, and because of its contribution to the overall prevalence of mental retardation, there has been considerable interest in attempting early behavioral interventions in affected children. Some of these studies have been poorly designed. Further, as new intervention strategies are developed, DS will remain a prime target group for clinical trials. These trials should be designed to produce epidemiologically generalizable results.

Prematurity/Low Birth Weight. Prematurity/low birth weight is associated with an elevated relative risk for a number of problems of pregnancy outcome. Rapid development of intensive obstetric and neonatal care and the increasing survival of smaller babies has made the problems of the very low birth weight baby (VLBW - less than 1500 Gm) more prevalent. While constituting only about 1 percent of live births, VLBW babies contribute a large proportion of infant deaths, and have the highest relative risk for handicaps in survivors.

Because prematurity/low birth weight is related to so many medical, behavioral, social and personal problems, a priority should be placed on studies which have promise in delineating etiologic factors and can therefore contribute to prevention. Much epidemiologic work has involved the repeated demonstration of relationships between low birth weight and such variables as parental socioeconomic status, maternal age, and birth order. But the biologic significance of such variables is poorly understood and deserves investigations which are directed towards understanding their meaning.

In addition to the need to do etiologic studies which can lead to preventive measures, it is important to study the consequences of premature birth better. Many such studies have been done on series from academic centers. We need more studies referable to defined total populations. Some types of studies will require long-term longitudinal treatment, in order to describe natural history and eventually definite outcome, and also to develop and test intervention strategies. Of particular importance is the determination of the prevalence in defined populations of the eventual developmental and physical outcomes related to specific treatments and factors: perinatal screening, electronic fetal monitoring, neonatal intensive care, cesarean childbirth use of tocolytic drugs and other medications during pregnancy, maternal alcohol usage, maternal occupation and maternal exposures to possible toxins. The end points of interest include mental retardation, epilepsy, learning disabilities, cerebral palsy, disturbed physical growth, and childhood physical morbidity.

Little attention has been paid to the epidemiologic relationships in a number of pathologic conditions associated with prematurity/low birth weight. A recent novel approach found some types of intracranial bleeding and neural damage increased in babies with prematurity/low birth weight, while other pathologic conditions had negative associations. While this work was based on an autopsy series, new imaging techniques can diagnose some of these problems in living babies. The further development of epidemiologic neuropathology shows promise for better understanding of events leading up to some types of MRDD problems.

It is often appropriate to ask the question: Is the problem the result or cause of prematurity/low birth weight? For instance, LBW occurs in excess among babies with Down syndrome. It seems clear that DS caused the LBW rather than vice versa. On the other hand, it is probably an unsettled question as to whether prematurity is the cause or result of the underlying factors involved in the development of spastic diplegia cerebral palsy. Studies also should differentiate, whenever possible, among prematurity (short gestational duration), low birth weight, and relative intrauterine growth (the relationship between gestational duration and birth weight).

The Etiology of MRDD: False Dichotomies. It has been traditional in the psychological literature to separate mental retardation into two etiological categories: that due to psychosocial variables and that due to biological causes. This descriptive framework flies in the face of modern epidemiological, psychological, and biomedical knowledge and methodology. The essential errors are that the etiology is assumed, and then an attempt is made to describe the prevalence in a nonanalytic framework. At the very center of the problem is an almost total absence of investigators with training in both the medical and nonmedical aspects of mental retardation and in modern analytic epidemiologic methodology. As noted above, clinical (both behavioral and medical), basic laboratory, and basic behavioral science and epidemiological expertise must be brought together.

Two additional dichotomies in investigations must also be eradicated. Epidemiologic studies commonly have used IQ of 50 as the dividing level for severe mental retardation, which is different from the criteria of the American Association on Mental Deficiency (AAMD). Whichever standards are used, it is clear that the use of IQ values with or without other behavioral characteristics fails to deal with the heterogeneity of mental retardation at any level. Future etiologic studies must deal with such heterogeneity.

The other dichotomy involves the separation of children into birth weight categories for follow-up studies. Recently there has been a concentration on very low birth weight infants (VLBW, 1500 Gm), and even separate categories of such infants. At the same time low birth weight babies (less than 2500 Gm) in older studies account for only about 20 percent of mentally retarded children, and for about half of the children with cerebral palsy. Little attention is paid to delineating etiologic factors in full weight and large weight babies who develop these and other conditions. With respect to epilepsy, for example, low birth weight babies may not be at higher risk.

Population Prevalence Studies of MRDD. The increasing utilization of intensive obstetric and neonatal care has resulted in the increased survival of smaller and smaller, and sicker babies. The contribution of this increased survival to the prevalence of developmental disabilities is not known, although some statistical models have been proposed for specific disabilities. Although data from the National Collaborative Perinatal Project may yield some answers, they are of limited relevance to the current situation, since in the intervening two decades obstetric and neonatal care have changed dramatically, and that series was not, as noted, ever representative of the general population. What is needed are population-based evaluations among survivors of modern obstetric and neonatal care of the risk of developmental disabilities, including mental retardation, cerebral palsy, epilepsy and learning disabilities, as well as other handicaps. It is important to assess these risks from a population perspective so that the benefits and the costs--personal, social, and financial--of present day care practices can be weighed. Such population-based studies are also essential: 1) to delineate risk factors of handicapping conditions; 2) to monitor obstetric and neonatal care; and 3) to plan for delivery of services.

Congenital Malformations: Undoubtedly evolving out of the thalidomide tragedy, with added impetus from the discovery of a number of other human teratogens and from experimental teratology, there has been an emphasis on the concept that maternal exposure to drugs and environmental chemicals is the

major cause of congenital malformations. This conceptualization belies the fact that each malformation which has been studied adequately shows a unique epidemiology, and that the major malformations of unknown etiology have been found in every population in which they have been sought, existing in a wide range of temporal, geographic, physical, climatic, sociocultural and genetic contexts. An alternative conceptualization holds that "natural" factors (e.g., genetic factors, nongenetic parental host factors, nutritional deficiencies) are the main factors in malformations of unknown etiology, as well as other problems of pregnancy outcome. Epidemiologic inquiry should take cognizance of both these conceptualizations.

The epidemiologic study of congenital malformations is hampered by inadequate data, because each malformation occurs uncommonly in most populations. Several data bases are maintained in different countries, but some are not population-based and therefore can be expected to suffer from biases of one sort or another. In a number of countries, malformations are reportable on birth and fetal death certificates, with varying degrees of accuracy and completeness. A small number of countries, such as Norway and Sweden, have national systems in which pregnancy outcome is linked to each parent by a permanent health service number. Most malformations are established in the first eight weeks of pregnancy, but women often do not seek care until this period has passed. Therefore data about exposures, illnesses, deficiencies, and the like must be obtained retrospectively, with all the inherent biases and inaccuracies. Clearly, there is need for establishing more accurate data bases, with particular attention to gathering accurate data from the beginning of pregnancy, or even before.

The field of experimental teratology has been useful in defining the pathogenesis of specific malformations. However, it is possible to produce a number of malformations in some experimental animals with a variety of drugs, and there are significant strain differences within a species with respect to susceptibility to teratogens, as well as interspecies variability. The most powerful human teratogen, thalidomide, does not produce malformations in some experimental animals, but does in monkeys. There is need to develop primate models of malformations. There is also need for the development of more predictive teratologic screening tests. There has been little collaboration between epidemiologists and teratologists, and much of the teratologic research has been done without reference to the known human data. It would seem profitable for epidemiologists and teratologists to collaborate in hypothesis generation and testing.

It has been proposed that surveillance of malformations can be enhanced by monitoring spontaneous abortions. Both morphological and chromosomal abnormalities are markedly increased among miscarriages. Further, memory bias for exposures and other events during pregnancy may be reduced. This issue deserves further consideration.

All definite human teratogens produce syndromes which, with perhaps one exception, are unique, and the syndromes produced are variable in manifestation. It has been pointed out that the epidemic of thalidomide embryopathy was not detected by the existing birth defects surveillance systems, due to classifications of malformations which were not sufficiently specific. In order to monitor human teratogens statistical/epidemiological methodology needs to be developed which can detect the occurrence of variable

syndromes. Perhaps the methodology of numerical taxonomy or a variation thereof may be useful in this regard.

Conclusions and Recommendations

Interdisciplinary research and research training needs to be fostered in order to develop a better understanding of the epidemiology of mental retardation and related problems. The first step should be convening of a conference to define the field and its problems. There should be broad representation among the various disciplines concerned with these issues. NICHD should foster the development of interdisciplinary research training programs which include epidemiologic training of behavioral and biomedical graduate and postgraduate students, both in clinical and basic science specialties.

NICHD should foster the development of the kinds of data bases necessary for rigorous and reliable epidemiologic studies of problems in the MRDD area. There are few adequate data bases in the United States or in other countries, and their unavailability inhibits the conduct of important epidemiologic research. Improved vital statistics data can serve an important function in epidemiologic investigations, as can data from Crippled Children's Services and special education programs. Other countries have successfully used a permanent health number which allows data linkage between offspring and parents.

It has been pointed out that the National Collaborative Perinatal Project of 1959-1965 was not representative of the American population of births during those years, and is not representative of the present American population of births. At the same time, that study has produced a number of insights into etiologic factors in poor pregnancy outcome and abnormal child development. It may be worthwhile to develop a successor to that study, now that obstetric and neonatal care have changed dramatically and new and more efficient epidemiologic and statistical methodology and data processing make really a representative study more feasible. It is imperative that longitudinal studies of development outcomes of specific parental risk factors and current obstetric and pediatric care can be done on defined American populations. Such studies should have the benefit of state-of-the-art diagnosis so that the heterogeneity within various cruder diagnostic categories can be minimized.

Epidemiologists and experimental teratologists are relatively unfamiliar with each other's work. It would be highly advantageous to have animal or other laboratory models which are translatable to the human condition. NICHD should sponsor research training and research which will help bridge the gap between laboratory models and the human situation.

Staff Commentary

Research on the epidemiology of MRDD is currently given high priority in Branch programming. Research training to prepare epidemiologists for research in the field of MRDD has lagged. Earlier, the Branch supported one training grant on the epidemiology of MRDD. It has since been eliminated in the strong competition for training grant funds. A replacement program is needed.

Data bases to support epidemiological work on MRDD are sorely lacking. Among other planned activities to improve the data available for study of MRDD, the Branch will give serious attention to epidemiologic data needs.

Action Steps

- o Convene a national conference on data bases to support reliable epidemiologic studies of MRDD (see also section XIII).
- o Hold a conference on behavioral teratology which involves epidemiologists (see also section V).
- o Issue a program announcement calling for submission of institutional training grants concerned with the epidemiology of MRDD (see also section XIII).
- o Initiate an epidemiological study to determine the incidence and prevalence of mental retardation in the United States.
- o Implement other recommendations more broadly through intensified staff programming.

III. DEVELOPMENTAL NEUROBIOLOGY

Research on nervous system development is of obvious relevance in searching for the causes of and ways to treat mental retardation and developmental disabilities. During human brain maturation 200 billion nerve cells will be generated. Each nerve cell will receive 10,000 to 200,000 connections and make the same or more connections. Failure of this developmental process at any stage can lead to brain dysfunction and disorders of the type this Plan is concerned with.

The Process of Brain Development: Current Knowledge and Knowledge Gaps

The process of brain development begins in the earliest stages of embryonic life and extends well into the second postnatal decade. With the exception of the cerebellum, a structure concerned largely with coordination of movement, the brain probably acquires its full complement of nerve cells (neurons) in the human infant prior to birth and perhaps as early as the beginning of the last trimester of gestation. While excellent data are available on the time of origin of many of the neurons in the monkey brain, little is known concerning the schedules of generation or the numbers of neurons produced in the embryonic and early fetal stages of human brain development.

Neurons constitute the fundamental information processing unit of the brain. Supporting cells or glia also play several crucial biological roles in facilitating neuronal operations and processes. In the mature brain, glia far outnumber neurons, but the period of maximal glial proliferation occurs somewhat later than the growth spurt period for neurons. What factors determine the relative numbers of glia and neurons and the extent to which early mechanisms of intercellular communication play a role in signaling functions in glia-glial and neuron-glial relations are unknown.

Once formed neurons must sometimes travel relatively great distances in the developing brain to reach the correct addresses in the neuronal subsystem for which they were originally specified by genetic programs. Research over the past decade has provided clues to at least two mechanisms of neuronal migration. Newly formed neurons at early stages in embryonic development produce long processes that arise from the ends of their cell bodies. One process anchors itself to the lining of the primitive ventricular cavity immediately subjacent to the germinative layers; the other process grows into the wall of the developing pallium (primitive cerebrum) until it makes contact with the outer surface membrane. In this way primary polar processes serve to anchor the primitive neuron to a particular site. There follows a process whereby the cell body, with its nucleus migrates to a position remote from its place of origin.

Migration of the cell body can also occur by movement of the cell body away from the early processes it emits. Both forms of neuronal migration must involve complex, temporospatial regulation of intraneuronal cytoskeletal elements that aid in the extension and directed growth of processes. Additionally, there must be continued incorporation of newly synthesized surface membrane constituents during the growth of processes. Once the correct address has been attained, extended processes must be

reabsorbed or transformed into other elements such as dendrites or axons during the subsequent phase of neuronal differentiation.

At this later stage of development, newly formed neurons undergo "free" migration to attain their correct position in the brain. Neurons destined for the cerebral cortex are aided in the migratory processes by the presence of specialized glial cells that span the thickness of the primitive pallium. The phenomenon encompasses a variety of progressively more complex problems. Time of origin, for example, is related to the neuron typology--that is, what kind of neuron the differentiated element will be. It is also related to the position the neuron will eventually attain in the cerebral cortex. But we do not know how the relationship between the neuron and glial cell is specified.

Nor do we know what factors guide the neuron to its proper location. For many years it has been argued that gradients of "chemical" signals in the external milieu of developing processes can influence directed growth by inducing the cytoskeletal system of the neuron to extend processes in the direction of increasing potency of the "signal." Alternatively it has been argued that a substrate of nonneuronal cells is first formed for "pioneering" processes, and additional processes follow the leading elements. Since faulty migration of neurons related to the loss of effective guidance by specialized glial cells is associated with disorganization and even neuronal attrition in subsystems involved in complex cortical functions, this is an important issue.

The orderly development of some parts of the brain and spinal cord depends not only upon the production and proper location of a specified number of neurons but also on the elimination of a variable proportion of neurons during and after the establishment of much of the circuitry of the nervous system. Much evidence has accumulated to the effect that programmed neuronal death is a prominent feature of developmental processes.

What we know about cell death during normal development indicates profound dependence of neurons on their targets. This interaction is characterized by the need of the classes of neurons for specific trophic agents, to which they are sensitive and other neurons (with other targets) are not. In two parts of the nervous system there is good evidence that the interaction is mediated by the protein nerve growth factor (NGF). NGF not only influences neuron survival; it also influences the direction of axonal and dendritic growth and local maintenance of terminal arbors. The current concept of the function of NGF as a trophic agent provides one of the central themes in developmental neurobiology. Understanding the rules governing mechanism of these agents is a major task for neurobiologists.

In addition to trophic agents like NGF, which go from targets to neurons, and neurons also influence the survival and maintenance of target cells. These trophic interactions are even less well understood, in part because no molecule has yet been identified that mediates them, and in part because they depend not only on chemical signals but on activation of the target cell as well.

For the most part neuronal proliferation and migration are early developmental events in the human brain, usually occupying the first half of gestation. Beyond the 20th week, neuronal differentiation, which includes the development of dendrites and axons, and the formation of synaptic connections dominates the developmental process.

The extensive dendritic systems of pyramidal neurons, the predominant cell type of the cerebral cortex, will eventually serve as surfaces for a variable synaptic input from other neurons.

In the human infant, dendritic branching patterns of most types of neurons in the cerebral cortex are established by the time of birth. Increase in segment length and terminal branching continue throughout the first and second year, and perhaps longer. Since dendrites of pyramidal neurons, provide 95 percent of the available membrane surface area for synaptic contacts, it is probable that factors which influence dendritic growth and development will significantly modify the functional activity of the cerebral cortex. Overt alterations in dendritic branching patterns and dendrite/soma volume ratios have been documented in immature laboratory animals in experimental hypothyroidism, phenylalanine loading, lead intoxication, fetal alcoholism, malnutrition, corticosteroid administration, X-irradiation, various genetic mutations, and environmental deprivation. These perturbations also exert a profound impact on the number, morphology, and distribution of dendritic spines, which are the small protuberances of dendrites that serve as one type of postsynaptic targets for presynaptic axons of neighboring and distant neurons.

Observations reported in recent years point to the vulnerability of dendritic spines in a wide variety of neurobehavioral developmental disorders associated with mental retardation. One of the striking observations relating to dendritic spine morphology has been made in examination of cortical neurons in a number of cases of developmental failure with profound mental retardation. In these cases the major abnormality involves structural features of dendritic spines, many of which retain fetal-like characteristics. Such observations suggest for examination the full range of processes governing dendritic spine maturation and the establishment of spine synapses.

A closely related problem has been disclosed in the discovery that profoundly retarded infants and children whose cortical neurons exhibit abnormal dendritic spines also show varicose transformations in dendrites that take on a "string-of-beads" appearance beginning with the most distal dendrite segments. Evidently a disorganization in the mechanisms of alignment parallel to the long axis of dendrites may be an important factor in the genesis of the dendritic varicosity, with subsequent alteration in dendritic spines and the loss of integrative properties of dendritic systems.

The problem of defining the fundamental mechanisms of neuron-neuronal and neuron-glial recognition was noted above in relation to neuronal migration and process formation. This problem is, in fact, a central issue in developmental neurobiology.

The specialized opposition between a neuron and its target cell (synapse) governs transmission and reception of information. There are no definitive answers to a major enigma in neurobiology--that is, how do neurons make and maintain appropriate connections? Although there have been heuristically valuable speculations based for the most part on "chemoaffinity" theories of one kind or another, these fundamental secrets of brain development remain unknown.

Regulatory mechanisms in synapse formation and operation are being studied in a wide variety of biological preparations and even in some artificial membrane systems. It is now appreciated that the nature of the target sought by a presynaptic element defines not only the number of synapses but also the functional type of connections and the nature of the chemical transmitter that operates the synapse. More than a quarter of a century has passed since the first definitive nerve growth factor for the development of sympathetic ganglia was identified in salivary glands and other tissues. Since then, growth factors have been shown to play important roles in regulating the metabolic machinery for cell differentiation, neurite growth, transmitter synthesis, and synapse formation.

The vast amount of work in the field of these so-called "trophic" agents raises the question of whether there are specific growth factors capable of influencing neuronal differentiation and synaptogenesis in the human cerebral cortex. In this connection, recent studies of neuronal storage diseases have revealed the presence of neuritic growth and secondary, but aberrant, dendritic differentiation on mature human cortical neurons laden with gangliosides and other complex metabolites. It should be emphasized that neuronal storage diseases are invariably associated with mental retardation and, in many instances, progressive neurobehavioral deterioration and death. There is evidence to suggest that intracellular accumulation of storage material per se is not the primary factor that leads to neuronal dysfunction. Hence, the mechanisms of neuronal geometry distortion, new neurite and synapse formation, and other factors that alter neuronal function must be involved.

One clue is the observation that, in early states of neuronal maturation, the dendrites of pyramidal neurons in the cerebral neocortex are capable of generating regenerative action potentials whereas dendritic action potentials are not normally observed in mature neurons. Development in this instance is apparently accompanied by a redistribution or loss of ion channels or other processes regulating impulse generation in dendrites of these cells.

The final stage in the development of the competent brain is the transformation of immature, slowly conducting pathways to high-speed conductile systems in accordance with specific requirements for rapid input-output information processing. This development is accomplished by proliferation of oligodendroglia and their activation to produce the insulating myelin that ensheaths axons except at bare sites called "nodes of Ranvier." At myelinated segments between these nodes, there is little or no current flow; hence, the conducted impulse speedily "jumps" from node to node.

Myelination is known to be delayed or disorganized by a host of factors including malnutrition, hypothyroidism, and inborn errors of metabolism, all of which are associated with mental retardation. It is now strongly suspected that axons must engage in some sophisticated signal interaction with oligodendroglia for the latter elements to wrap extended portions of their cytoplasm around a number of different axons. But we do not yet know what these signals are or how they are regulated nor what mechanisms control the formation of nodal membrane in the axon with its high density of transmembrane ion channels.

This brief survey would be incomplete without consideration of one of the most intriguing questions in contemporary neuroscience: Is the brain modifiable? That the brain is functionally modifiable seems self-evident from even a casual consideration of cognitive development in infancy and childhood. An early period of plasticity in the establishment of the functional and structural integrity of the visual system in cat and monkey has long been established. An imbalance in visual input in subhuman primates up to a certain period postnatally, approximately three months, results in significant morphologic and physiological changes in neurons at subcortical and cortical sites. Evidently the monkey's visual system undergoes "hardwiring" after this period and is no longer significantly modifiable by sensory deprivation thereafter. While early monocular visual deprivation produces profound deficits in binocularly driven neurons of visual cortex, reverse suture before the end of the critical period leads to reactivation of cortical synaptic pathways driven by the previously deprived eye. This reactivation is indicative of a remarkable degree of modifiability of initially genetically programmed neuronal circuitry in the primate brain in the early postnatal period. A host of other studies has demonstrated varying degrees of modifiability of developing as well as of some mature systems in the mammalian brain. One may envision a series of discrete critical periods for different "hard-wired" functions, such as initial visual and auditory information processing and perhaps greater plasticity for the establishment and validation of cognitive processes in the developing human brain.

It has long been known that lower vertebrates, such as fish and amphibia, possess a remarkable potential for regeneration of different parts of the central nervous system. Recovery of certain motor functions following damage to the motor system in immature monkeys is rapid and virtually complete, in contrast to similar damage in adult animals. But why this is so has escaped adequate explanation. Whereas previously neuroscientists were detailing the reasons why brain neurons could not regenerate or sprout new axons and synapses, they are now recording all the conditions in which axonal sprouting and new synapses can be achieved. The question is no longer, "Why don't mammalian central neurons regenerate axons and synapses?" but rather, "what are the factors preventing axonal regrowth after injury?"

The problem of brain modifiability is not exclusively a problem of damaged axons sprouting new collaterals and synapses. For example, recovery from frontal cortex lesions in infant monkeys is associated with new connections that form between intact cortex and certain subcortical structures. It has also been shown that training infant monkeys before they sustain frontal cortical lesions can greatly facilitate recovery of

functions involving the damaged cortex. Here behavior is in some fashion facilitating mechanisms of functional recovery. We do not, as yet, know how modification of brain function should receive attention in mental retardation research.

Before concluding this brief survey, it should be noted that much neurobiological research depends on the availability of techniques for noninvasive tissue visualization and in-situ metabolism. A particularly exciting development in this area is the extension of magnetic resonance imaging (MRI) instrumentation to computer tomographic (CT) imaging. In x-ray CT imaging it is necessary to expose the subject, human or experimental animal, to appreciable radiation dosage and to utilize contrast media. In contrast, MRI spectra depend on the particular atomic nucleus that is resonant, most often the naturally abundant isotope of the element.

Brain has areas of high and low lipid content, which makes it an excellent tissue for imaging, particularly in applications related to brain development and impaired brain development. Many inborn errors of metabolism, for example, involve lipid perturbations that affect normal brain development and function. The MRI technique permits longitudinal studies of this altered imaging and spectroscopy with a potential for spatial resolution of anatomic detail approaching a submillimeter or less.

It should also be noted here that a number of animal models with defects analogous to those of humans provide an excellent basis for studying human problems (see Section V for further discussion of criteria for selection of suitable animal models). For example, there is a rat model for PKU; a siamese cat strain with an arylsulfatase deficiency; mouse and dog models for galactosyl ceramide lipodoses; a twitcher mouse for globoid leukodystrophy; and cat model for Hurler syndrome. These animal systems can be used as both imaging and spectral studies of brain development concurrent with spectral and kinetic studies of energy production and specific metabolite fats.

Priority Areas for Future Research

Recent years have seen a tremendous increase in our knowledge of the development of the nervous system. As the foregoing discussion makes clear, much of this progress has involved moving from phenomenological studies towards work on the cellular and molecular bases of development. It is equally clear that much remains to be done and four major areas merit priority attention. Each is discussed briefly in turn.

Determination of Phenotype. How cells decide which pathway of differentiation to follow is a central problem in developmental biology. This question is especially prominent in the nervous system given its enormous cellular heterogeneity and the multitude of characteristics that make up each phenotype (the number, size, and shape of axons and dendrites, the type and distribution of receptors, etc.). Considerable progress has been made regarding control of phenotypic expression in certain neural crest derivatives. In vivo transplant studies in embryos have shown that the developmental fate of neural crest cell populations is subject to local environmental signals; these cells can adopt any of

several different phenotypes, depending on where the cells are placed. At least some of this plasticity is maintained after the cells stop their migration, form ganglia, and cease mitosis. For instance, adrenergic neurons can be converted into cholinergic neurons by adding a protein purified from certain cholinergic target tissues. Manipulation of the hormonal milieu or activity in the neurons can also control transmitter decisions. Thus, the environment surrounding developing neurons is even more important than previously recognized--controlling not only neuronal life or death, but also their phenotype.

Technological innovation in molecular genetics has evoked a wave of optimism in developmental neurobiology. At what stage a given characteristic is turned on or off can now be analyzed at the mRNA level instead of at the level of the protein product. It should be emphasized, however, that obtaining the gene sequence and observing the timetable of message appearance will not immediately solve the cell biological questions of development. The problems of which cell interactions are important, the identification of the intercellular signals being used, and the nature of the transduction of those signals are questions that will not be immediately solved by knowledge of DNA sequences.

Axonal Outgrowth and Target Recognition. Culture studies have shown that the initiation and the direction of process outgrowth, can be controlled by diffusible and surface-bound molecules. The nerve growth factor can act at the tip of the axon and alter the direction of its growth in a chemotactic fashion. Partially purified molecules associated with proteoglycans can elicit neurite outgrowth from many different types of neurons. Such surface-bound factors can also guide the direction of growth cone movements in culture as well as the direction of regenerating motor neurons in vivo. A novel method of monoclonal antibody production has recently enabled the isolation of several antibodies which directly block one of these neurite outgrowth promoting activities. Such antibodies should prove useful both in the purification of the molecules and the histological localization of these activities in the developing embryo.

There has also been progress in the area of identifying potential "recognition" molecules. Cells from a variety of embryonic tissues, including various parts of the nervous system, can aggregate specifically with one another after dissociation. Several molecules which mediate such aggregation have been purified and partially characterized. Although it is not completely clear what this aggregation phenomenon is telling us about development, antibodies against them have been shown to disrupt fiber-fiber interactions between growing neurites as well as the migration of embryonic neural retinal cells to their appropriate layers.

Information concerning the molecular nature of the growth cone itself is almost completely lacking. While there have been a number of morphological studies, very few groups have attempted to characterize biochemically these key structures where growth and choice of direction takes place. The major problems are isolation without contamination and lack of sufficient material. This is an area where considerable effort is needed.

Neuronal Cell Death. Throughout the vertebrate central and peripheral nervous systems about half the neurons generated in early embryonic life die. In recent years it has become increasingly clear that the death of any given neuron is not entirely programmed, but rather the process involves competition between neurons in a struggle for survival. Limb excision and transplantation studies suggest that the competition is for growth factors produced by target tissues. Experiments in cell culture have demonstrated that all of the neurons which would have died can be rescued in culture if appropriate levels of the growth factor are supplied. Furthermore, it appears that different classes of neurons may each require a different, specific factor. Such factors have been purified for sympathetic and certain sensory neurons, and studies are in progress on growth factors for parasympathetic, motor, and various brain neurons.

Since neuron death is a key feature of many neurological and neuromuscular diseases, accidents leading to paralysis or death, and syndromes caused by drugs, alcohol, and other toxic agents, it clearly is of importance to identify the appropriate growth factors and to investigate their potential use in damage repair and regeneration. Progress in this area will necessitate large-scale, expensive purification efforts, the use of state-of-the-art monoclonal antibody technology, and considerable improvement in culture systems for the growth of identified populations of CNS neurons.

Exogenous Influences on Neural Development. A classic example of exogenous influence on neural development is the mental retardation associated with hypothyroidism. Pathologies in insulin, growth hormone, and glucocorticoid production can also have global deleterious effects on the developing nervous system. More recently, certain hormones have been found to exert specific effects on particular areas or cell types in both the central and peripheral nervous system. Sex steroids also cause dramatic and selective alterations in brain development. Anatomical studies have revealed gross structural differences between male and female brain and spinal cord. These differences have been shown to be the direct result of sex steroid levels in the developing animal, and the neurons can respond by increased growth in culture. Furthermore, in several cases it has proven possible to alter not only the size of the specific brain areas by hormonal manipulation, but to thereby elicit or suppress a sexually dimorphic behavior. These insights into the control of behavior by extraneural agents, and the gross plasticity of the brain, are important for the study of learning and memory.

Sensory Input. The sensory environment of the organism, like extraneural agents such as hormones and growth and differentiation factors, controls neural development. Sensory input of many modalities controls neuronal differentiation and survival. It appears that competitive interactions occur between developing neurons, and activity induced in these cells controls whether they keep or withdraw synapses previously made. Such competition between synaptic inputs appears not only with experimental manipulation, but it is known to be a normal part of development which depends on appropriate exteroceptive sensory input. One area for future work is the molecular basis for this competition. The other side of synapse elimination phenomenon is sprouting, and a protein which promotes

it has been tentatively identified on gels. Also, an antiserum has been produced which blocks sprouting. It would not be surprising if hormones and other substances (neuromodulations, neurotransmitters) could also play a role in these synaptic rearrangements.

Conclusions and Recommendations

Magnetic resonance Imaging (MRI) for brain imaging and metabolic studies in humans and experimental animals should be stressed. MRI studies do not entail X-radiation exposure, and imaging can be obtained at magnetic field levels well below those which produce ill effects in experimental animals. The technique has already produced major advances in the study of human white matter disease and other disorders such as tuberous sclerosis. In experimental animals, where higher magnetic fields can be used, resolution at the micrometer level is anticipated.

In addition to its value as an imaging technique, MRI provides the exciting possibility of monitoring energy metabolism in "real time" in the living organism. This technique has already been applied in infants suspected of suffering from anoxia, and in human muscle diseases. Many further advances are expected in the near future and will be applicable to humans and animal models.

Availability of experimental models of human disease should also be encouraged, with emphasis on animal models of inherited neurologic disease and on tissue culture techniques, particularly those which utilize serum-free totally defined media. Over 200 animal models of human genetic disease are now known. Many of these disorders in animals affect the nervous system and have been shown to be close counterparts of a human disease. While the need for animal models has been recognized in the past, the more recent awareness that specific therapies may indeed become a reality has made the availability of these animal models an absolute necessity. Only in such systems will it be possible to evaluate the effectiveness, risks, and indications of different forms of therapy. The identification, study, and maintenance of these models is important to progress in the field.

Tissue culture systems have already proven their value for the definition of disorders such as the mucopolysaccharidoses, and are now being used to identify the molecular mechanisms that underlie enzymatic defects. Yet, it is recognized that their potential is much greater still. Particular promise is seen in the use of serum free culture systems, where all elements that influence the culture can be identified exactly. Another area of great promise is the increasing capacity to culture nerve cells, Schwann cells, and glia.

Study of the factors that control nerve cell growth and interactions is crucial. Recent years have seen exciting advances in our understanding of factors that control nerve cell growth and interactions. Understanding of these factors is fundamental to understanding how environment and its possible manipulations affect nervous system development.

Studies in tissue culture systems, combined with advanced microchemical techniques and use of monoclonal antibodies have begun to identify the

neuronotropic growth factors, hormones, and signals that are responsible for cell sprouting and synapse formation. Continued advances require support of basic work in neuroanatomy, neurochemistry, neurophysiology, immunology, and behavioral sciences, with emphasis on multidisciplinary research and the training of scientists with sufficient expertise to utilize these diverse approaches effectively.

The nervous system, perhaps more than any other tissue, is rich in membranes with a great diversity of structure and function. Greater knowledge about membrane structure and function is required for an understanding of nerve impulse transmission, cell-cell interactions, neurogenesis, synaptogenesis and receptor function. To achieve additional progress better methods are needed to isolate well-defined membrane preparations, the isolation of different cell populations in culture, particularly in chemically defined media. Another important topic is the study of the biologically active components derived from membranes, particularly the oxygenated metabolites of polyunsaturated acids which may have a role in the deleterious effects of anoxia, injury, and aging.

As is true of all fields of medicine, molecular genetics and recombinant DNA techniques (see Section IV for a more extended discussion) are key to most aspects of developmental neurobiology. They are indispensable to the identification and understanding of the many dominant neurodegenerative diseases that take such a heavy toll in loss of human potential and suffering. These techniques are required if we are to gain understanding of the factors that control the formation of the estimated 100,000 different enzymes, receptors, and structural proteins contained in the brain cell. Clearly, research in this field also deserves a high priority.

Staff Review

Developmental neurobiology is a prominent component for research support within the MRDD Branch portfolio. In the judgment of MRDD Branch staff, particular attention should be paid the elucidation of Rett Syndrome, a baffling and progressive neurological dysfunction. This condition has been described in all races and all parts of the world and so far seems restricted to females. The Rett Syndrome represents a biologically based behavioral phenotype and provides an excellent opportunity to learn more about the neurological basis of behavioral disturbance. The NICHD-NINCDS jointly-sponsored Second International Workshop on Rett Syndrome held in November 1985, provides an excellent basis for further work.

Action Steps

- o Issue an RFA for studies of the factors that control nerve growth and interactions.
- o Issue a program announcement on the development of experimental models with emphasis on animal models of inherited neurological disease.
- o Issue an RFA on Rett Syndrome.
- o Encourage regular programming, in coordination with NINCDS, in the areas emphasized in this section of the Research Plan.

IV. GENETICS, CYTOGENETICS, AND INBORN ERRORS OF METABOLISM

Genetic disorders have become increasingly more prominent in the etiology of human disease. This phenomenon is a consequence of advances in medicine and surgery, and the application of public health measures, such as improved nutrition, availability of antimicrobial agents, and immunization programs, which have reduced the contribution of environmental factors and infectious diseases in human mortality and morbidity. In recent surveys of pediatric hospital admissions, 22-31 percent of patients have a disorder identified as at least partially genetic and 7-11 percent have a disorder which is entirely genetic in origin.

Current Knowledge

Geneticists and cytogeneticists have made major progress over the last two decades in identifying the type of inheritance, clinical manifestations--and in a subset of them the specific chromosome or gene--of a large number of genetic diseases associated with mental retardation and developmental disabilities. About 40-60 percent of currently known causes of moderate to severe mental retardation are now known to have a genetically determined component. These include chromosomal abnormalities, inborn errors of metabolism, some abnormalities of the central nervous system, multiple congenital malformation syndromes caused by single genes, other syndromes of unknown etiology which follow known patterns of inheritance, and those with a hereditary component that are environmentally influenced.

The causes of milder mental retardation are less frequently specifically identifiable but more frequently familial. This type of so-called "social/cultural" mental retardation affects approximately two-thirds of the mentally retarded population. Relatively little progress has been made in the clarification, management, or even delineation of the extent of the problem in this large population group.

MRDD-Related Genetic Disease. Geneticists and cytogeneticists, together with molecular biologists, have recently made a number of spectacular advances which have enormous potential for further elucidation of the underlying basis of some MRDD-related diseases. These advances will lead to an increasing number of prenatally diagnosed fetuses, greater possibilities for carrier detection, and the potential for curative rather than symptomatic medical management.

One of the most common, and the most readily identifiable, genetic conditions found among the mentally retarded is Down syndrome. Although demographic shifts in the U.S. population brought about a decrease in the frequency of Down syndrome, it remains the most common chromosomal aneuploidy of human liveborns and one of the leading known causes of mental retardation. It is associated with hearing abnormalities, and congenital heart disease. The primary genetic abnormality in Down syndrome is known to be trisomy 21. It is also known that the risk of bearing a child with Down syndrome increases dramatically with advancing maternal age.

About 95 percent of individuals with Down syndrome have trisomy 21 due to a meiotic nondisjunctional event. This type tends to occur by chance to parents whose chromosomes are normal, and in general the statistical recurrence risk (to the parents only, not to other family members) is only 1-2 percent. This

risk, however, is a composite of two very different risks. The vast majority may carry no increased risk. But a small group may be at increased risk for any nondisjunctional event (a "gene" or tendency toward nondisjunction can be postulated), or for recurrence of the same kind of nondisjunction because of a low degree of parental mosaicism, i.e., a few cells with an extra chromosome. It is currently not possible to distinguish a priori among families in the different groups--hence, the empiric recurrence risk of 1-2 percent. Attempts are currently underway to identify, with cytogenetic techniques, individuals who are at higher risk for nondisjunction. In the remainder of cases (less than 5 percent), Down syndrome is due to a chromosome rearrangement called a translocation. Half of those are inherited from a carrier parent. Parental karyotypes can identify the carrier and related carriers in the family. The other half occurs de novo and is not inherited. Current research at the molecular level has localized several genes to chromosome 21, and is beginning to clarify some of the aspects of Down syndrome in more detail. In addition, premature aging in Down syndrome and its relevance to Alzheimer's disease is a broad area of current research. (The education potential of Down's syndrome children is also a major item of current research, see Section XI of the Plan).

A second common identifiable group of genetic conditions associated with mental retardation are those caused by an abnormality on the X chromosome. The significant excess of males among the inmates of mental retardation institutions has been recognized for about 50 years. But it was not until the 1970s that the partition of X-linked recessive genes was suspected in the etiology of nonspecific mental retardation. Since then, the heterogeneity of X-linked mental retardation has become increasingly obvious. There is now known to be a large number of genes associated with mental retardation on the X-chromosome, and the progressive discovery of additional forms of X-linked disorders is a major reason for the falling proportion of cases of MRDD with unknown etiology.

The most common type of X-linked mental retardation, for which there is a specific laboratory test, is the fragile-X type. A proportion of males with X-linked mental retardation was found upon cytogenetic investigation to have a fragile site on the short arm of their X-chromosome. This is now known to be on X_p28. It can constitute a valuable genetic marker when it is found in affected males and some carrier females.

Two other major forms of genetically-determined mental retardation are inborn errors of metabolism and some central nervous system abnormalities. These are important because they lead to devastating and potentially lethal disease.

Inborn errors of metabolism are almost always caused by defective genes. Biochemical advances have done much to elucidate the effects of these diseases if not treated, and newborn metabolic screening programs now contribute to the prevention of the devastating effects of some of them. In particular, Phenylketonuria (PKU), an autosomal recessive disorder, can be successfully diagnosed within a few weeks of birth. Treatment of genetically affected infants with a low phenylalanine diet has largely prevented or mitigated the disastrous consequences of PKU. In the past, virtually all phenylketonuric patients were severely mentally retarded and few reproduced. Over the past 20 years, however, routine newborn screening and early dietary treatment of affected infants have resulted in normal physical and intellectual development

among individuals with PKU. Many of these have already reached, or are approaching, the child-bearing period. It is well known that the offspring of PKU women, while not phenylketonuric, tend to be mentally retarded, microcephalic, and otherwise malformed. The prevention of mental retardation through the implementation of diet prior to conception and throughout pregnancy is currently the subject of collaborative research. Molecular genetics has made spectacular progress in the identification of DNA segments (see further below) in the vicinity of the genes of some metabolic disorders, thus enabling prenatal diagnosis, carrier detection, etc. in some informative families. PKU is a paradigm of such a disorder. Neither replacement nor other causative therapy is currently available for most metabolic disorders.

There is a group of individually rare but cumulatively relatively common (approaching one percent) multiple malformation syndromes associated with mental retardation. Some of these are inherited in a Mendelian way (e.g., Smith-Lemli-Opitz syndrome), others are thought to be sporadic or uncertain (e.g., Williams Syndrome, some cases of Prader-Willi syndrome). Neither the natural history nor the variation in expression of physical, cognitive, and other symptomatology is known for most of these. Little anticipatory guidance is available for families. Much molecular research is needed before the genes for at least the Mendelian syndromes can be localized.

Neural tube defects occur in about 1 to 3 per 1,000 newborns. The incidence varies geographically. Patients with neural tube defects include those with anencephaly and those with myelomeningoceles. Most are detectable prenatally through alpha fetoprotein screening and ultrasound investigation. Research is currently underway in an attempt to determine causes of neural tube defects. Many environmental as well as genetic factors have been implicated, including vitamin deficiencies in mothers. Neural tube defects are a characteristic paradigm for a single isolated birth defect of multifactorial etiology, the elucidation of which could point toward analogous solutions for other such conditions.

Yet another group of disorders associated with mental retardation which merits further attention is the neurocutaneous disorders (e.g., tuberous sclerosis, neurofibromatosis, incontinentia pigmenti, etc.). Most are inherited in an autosomal dominant way with a well-known 50 percent risk that any offspring of an affected individual may also be affected. However, dominant disorders, whether autosomal or X-linked, are fraught with pitfalls for the genetics counselor. Issues to be considered include spontaneous mutations, variable expressivity, genetic heterogeneity, and others. Each of these merits an independent research approach comparing molecular, phenotypic, pedigree, medical, pathological, and other aspects.

Technical Advances. Major advances in human genetics have come in the last decade and a half in the area of prenatal diagnosis. Transabdominal amniocentesis in combination with ultrasonography is the most widely used technique. A wealth of information can be derived from studying material of fetal origin—amniotic fluid cells and the fluid itself. Chromosomal, open neural tube and other defects, and other structural abnormalities are becoming increasingly more easily identified. Amniocentesis can be done safely and effectively at 15-16 weeks gestation. Prior to amniocentesis, ultrasonography is used to verify gestational age, determine placental and fetal positions and number of fetuses, and detect gross fetal malformations. There are some disorders where

it is not possible to identify a specific abnormality; if they are sex-linked, fetal sex determination is the only option (e.g., those types of sex-linked mental retardation that are not characterized by the fragile-X). The applicability of current antenatal diagnostic techniques depends on knowledge of the etiology at the chromosome level, the molecular level in some dynamics of the disease.

Recent advances in molecular genetics and gene mapping are very promising. Genes are segments of the DNA molecule containing the code for a specific function, which are located linearly on the chromosomes. Traditional diagnosis of genetic diseases using biochemical approaches is dependent on the gene in question being expressed in the tissue available for analysis. New recombinant DNA techniques free analysis from this constraint. All nucleated cells contain a complete copy of the genomic DNA, so globin genes can be studied in skin fibroblasts, lymphocytes, or the chorionic villi of the early conceptus (about which more below). These can then be reproduced (cloned) to produce multiples of the identical gene. Thus direct analysis of DNA allows one to describe the genotype directly rather than having to deduce it from the phenotype.

The ideal for elucidating genetic disease would be to have a complete gene map of all the chromosomes, with the exact position of every gene on every chromosome determined in relation to the other genes located on its chromosome. We are still far from such a situation, but the new DNA techniques are exploding the rate at which gene assignments are being discovered. In 1973, for example, 64 gene assignments were known. By 1985, the number had grown to 1,300, with a rapidly increasing rate of identification since direct analysis of DNA became possible.

These advances hold great promise for more sophisticated and wider ranging antenatal diagnosis. They also hold promise for developing genetic markers to identify carriers of the abnormal genes either directly or by identification of stretches of DNA close to them. Finally, they hold promise for treatment of the underlying defect in some genetic disease through direct gene therapy. Each is discussed briefly in turn.

The new technique of antenatal sampling that will be able to exploit these advances in gene identification is chorionic villi sampling (CVS). This is transcervical sampling of chorionic villi at 9-11 weeks gestation. Providing this technique is proven to be as safe as amniocentesis (and its safety is another important area for research), this approach will offer many advantages for antenatal diagnosis. CVS is applicable much earlier in pregnancy than amniocentesis and thus may be more acceptable to patients and to the general public. Further, chromosome analyses may be obtained within a few hours to a few days, as opposed to the approximately two weeks required for culture of amniotic fluid cells. Finally, the amount of cellular material obtained for the application of recombinant DNA studies is larger than obtainable from amniocentesis.

Molecular techniques are now enabling identification of healthy carriers of some recessive genes in asymptomatic individuals. This is possible through identification of stretches of DNA that are close enough and can serve as linkage markers for the diseased gene, since they are inherited together (linked) most of the time. One promising technique (mentioned earlier) is

that using restriction fragment length polymorphisms (RFLP); these occur naturally in all individuals, and do not cause abnormalities in the very great majority of known examples. Once even a weak linkage permitting a chromosome assignment is detected, the search for RFLPs can be made quite efficient by concentrating on cloned DNA sequences that are known or found to be in the vicinity of the first linkage marker found.

Therapy to correct a specific genetic defect is perhaps the most important long-term promise of the new DNA-related advances. Gene therapy refers to the introduction of a normal, functioning gene into a cell in which that gene is defective. Research advances in recombinant DNA techniques, gene isolation and characterization, somatic cell genetics, virology and molecular biology make it potentially possible to apply gene therapy in a number of lethal genetic disorders. Single gene diseases with no effective therapy are reasonable models for attempts at gene therapy. In vitro and in vivo studies (mostly on rodents) have shown that gene transfer can be successfully carried out. For example, a full-length cDNA clone of human phenylalanine hydroxylase (PAH), the defective enzyme in phenylketonuria, has been inserted into a eukaryotic expression vector and transferred into a special type of mouse cells which do not normally express the PAH. The transformed mouse cells expressed PAH messenger RNA, immunoreactive protein, and enzymatic activity that are characteristic of the normal human PAH. A study is currently underway to develop gene transfer methods for the treatment of the Lesch-Nyhan syndrome. The syndrome is an X-linked disorder characterized by varying degrees of mental retardation and other pathological symptoms which inevitably lead to early death. The condition is due to the absence of an enzyme, hypoxanthine guanine phosphoribosyl transferase (HPRT). Investigators have developed a viral vector containing a functional human cDNA clone of HPRT. Infection of human lymphoblast cells devoid of HPRT, with this vector, has been proven to lead to the conversion of those cells to express HPRT.

Priority Areas for Future Research

Although much has been learned, and at an increasing pace, about the associations of genetic disease and mental retardation and about the role of defective genes in human disease more generally, much remains to be done. The proportion of cases of mental retardation of unknown etiology is falling; but that very fact indicates the need for continuing research to reduce the proportion further and to direct efforts toward therapeutic strategies.

This search should place particular emphasis on the occurrence of heterogeneity and the possibility of partial expression. With respect to the latter, it is highly likely that as methods of detection and diagnosis improve, the incidence of at least partial expression of underlying disorders will increase, and that the patterns of partial expression will allow further elucidation of the underlying inheritance pattern of some diseases.

A particularly fruitful area in this regard is X-linked mental retardation. Although some types of X-linked mental retardation exhibit the fragile-X which is cytogenetically visible, others do not. In addition, some males with the fragile-X do not express mental retardation. Further, some of the obligate female carriers do not exhibit the fragile-X (with indications that its visibility sometimes decreases with age, and its presence may be inversely correlated with the intelligence of the female). The fragile-X phenomenon is the only X-linked disorder the location of which is known on the X chromosome,

although the gene itself remains elusive. Currently, many other types of X-linked mental retardation are known with no identified locus for the defective gene. Since the X chromosome is well mapped and polymorphisms are available for most of its segments, families with nonfragile-X types of X-linked mental retardation are a promising group for research.

With the help of these new techniques, it will be possible to follow the genetic defect through several generations of families and to distinguish affected individuals from unaffected ones and identify carriers. On the assumption that nonexpression of fragile-X, for example, is confirmed, it will be necessary to determine the factors which limit expression. In order to exploit the potential of the new DNA diagnostic procedures, DNA samples from large and well studied families with the several forms of X-linked mental retardation should be deposited in a nationally supported cell bank (see further below). Carefully planned studies of the prevalence of the fragile-X and other forms of X-linked mental retardation are needed. In addition to molecular investigations, various anthropometric and other clinical studies including CAT scans, autopsies, longitudinal assessments, racial and ethnic assessments, etc. should be encouraged. It is also of utmost importance to evaluate the efficacy of therapy with agents such as folate. The evaluation of response to therapy will necessitate a better delineation of the phenotype of the syndrome. In particular, improved means for assessing the behavioral aspects of the syndrome are required.

Down syndrome is another priority area for further research. As noted, the risk of bearing a child with Down syndrome increases dramatically with advancing maternal age. The reason for this association is still not known. It has been proposed that differences in the processes of oogenesis and spermatogenesis are responsible for increased frequencies of nondisjunction in older mothers. The entire complement of oocytes in a human female is formed well before birth. Thus, the oocytes ovulated by a 35-year-old woman have been in meiotic stasis for more than 35 years. In human males, spermatocytes are not produced before puberty and are thereafter generated in a continuous cycle of relatively short duration. This difference may increase the vulnerability of the oocyte, compared to the sperm, to the effects of noxious agents over a longer period. An additional influence which may be contributory is a decreased rate of spontaneous abortion during the first and second trimesters of aneuploid conceptus by older mothers. All these hypotheses have been formulated for many years. It is frustrating that further progress has not been made.

Although the primary genetic abnormality in Down syndrome is known to be trisomy 21, the mechanisms whereby an abnormal karyotype results in an abnormal phenotype are unknown. Recently, investigators have observed that fibroblasts obtained from lungs and endocardial cushion structures of abortuses with trisomy 21 are more adhesive in vitro than age-matched controls. Using anatomic studies and computer simulations, they demonstrated how increased adhesiveness might interfere with pulmonary development and endocardial cushion formation in Down syndrome individuals. They hypothesize that increased adhesiveness is mediated by cell surface proteins coded on chromosome 21 which are present in triplicate in Down syndrome individuals. Further insights into the mechanisms by which mental retardation occurs in Down syndrome may be obtained from studies of animal models, preferably mammalian model systems in which close genetic homology is maintained for the genes on

the Down syndrome region of human chromosome 21. Such a model has been developed in the mouse with trisomy 16.

Another priority is the need to develop a national bank of recombinant DNA probes of importance to research in mental retardation. Mention has been made of the expected contribution to our understanding of chromosome behavior from the isolation of DNA segments from chromosome 21. DNA segments isolated from other chromosomes and particularly from aneuploid patients would have comparable value for research in this aspect of mental retardation. A nationally supported bank of probes, analogous to that for cultured human cells, should be developed.

The large number of recombinant DNA probes that are now available, and the certainty that the number will be rapidly augmented in the near future, also provide the opportunity to increase our knowledge dramatically of the human gene map. This information will support research directed toward understanding chromosome behavior in a major way, as well as delineating inherited forms of mental retardation. The time is ripe for major support of gene mapping activities.

Some progress has been achieved in developing animal models relevant to mental retardation research (such as trisomic mice). The progress has nonetheless been limited, because we have insufficient understanding of the homology between the human and nonhuman genomes. The human recombinant DNA probes can be expected to clearly delineate the extent of the homology between the human and, for example, the mouse genome.

With respect to the genetic disorders which are inborn errors of metabolism, the complexity of intracellular malfunction remains a barrier to new therapeutic attempts at enzyme replacement. Continued research is needed to explain single metabolic defects in terms of abnormal or absent activator proteins; in terms of disorders of intracellular processing including defective conversion of proenzyme to enzyme; in terms of compartmentation of enzymes at the surfaces and within subcellular organelles; and in terms of the physical heterogeneity of altered proteins. The regulation of intracellular processing and compartmentation is of obvious import in developing rational therapeutic strategies. In addition, much has been learned about the specific nature of protein defects, but very little about the specific pathophysiologic mechanism by which these defects bring about cerebral dysfunction. The inaccessibility of the tissue justifies the encouragement of research to develop and investigate animal models and in the use of noninvasive new technologies such as nuclear magnetic resonance and positron imaging. Continued and vigorous research in the field of lysosomal storage diseases also is needed. These conditions are perceived as being particularly relevant to mental retardation and to the deployment of techniques using recombinant DNA, the investigation of intracellular sorting mechanisms, the use of animal models and enzyme replacement therapy. Finally, although early work in enzyme replacement has been disappointing, since therapy and prevention are the ultimate goals of research, studies specifically oriented to treatment need to continue. This is likely to vary from organoleptic improvements in diet, to the role of new noninvasive technologies such as NMR and PET scanning, to the complexities of inserting genetic material.

Gene therapy of somatic cells, as is clear from the discussion in the preceding subsection, is an extremely promising long-term strategy for treatment of the underlying basis of some genetic disorders. Work in gene therapy should be strongly encouraged. Diseases that are promising candidates are defects of a single gene which has been identified and for which the normal gene has been isolated and cloned. It is generally acknowledged that before human gene therapy is attempted, the following conditions should be met for each gene introduced: the new gene can be delivered into the affected cells and will remain there; the new gene does not harm the cells; and the new gene can be regulated appropriately.

The medical needs of mentally and developmentally retarded populations (as their survival rates increase and they move into adulthood) constitute a neglected field which urgently needs clarification. No one really knows the clinical course of genetic diseases. A 50-year-old Down syndrome patient, for example, has an extra chromosome. This chromosome can be expected to affect the susceptibility to disease, the effect of drugs routinely given for conditions unrelated to the syndrome, and so on. General medical management of adult mentally retarded patients with single gene, chromosomal, multifactorial, and other disorders all too often proceeds in the dark. The natural history of many disorders associated with mental retardation is unknown and should be explored.

Finally, more and more persons who are mentally retarded are reaching adulthood, living lives in the community, and reproducing. The issue of the extent and details of the risk of mental retardation in their offspring urgently needs elucidation. It is known that, as a group, they bear children whose IQs have a strong tendency to regress toward the mean. This makes any general statement about the dangers of reproduction for the group as a whole inappropriate. Research is urgently needed to refine and make more precise the reproductive risks of the wide variety of mental retardation whose etiology is consistent with human development into adulthood.

Conclusions and Recommendations

Recent advances in gene identification and recombinant DNA indicate that gene identification should be given high priority, as well as new techniques of antenatal diagnosis and basic research into the potential for somatic cell gene therapy.

There is also a continuing need for research into the hereditary patterns, etiologies, natural history, variation in expression, and medical management of the many genetic or partly genetic disorders associated with mental retardation which are still poorly understood. Specific areas for study include:

- o X-linked mental retardation, in particular heterogeneity and the likely possibility of partial expression.
- o Down syndrome, in particular the reason for increased risk of nondisjunction and the factors likely to influence that risk.
- o The riddles of partial expression, particularly in the neurocutaneous disorders.

- o The problems of PKU offspring, in particular the level at which serum phenylalanine dietary restriction should be maintained during pregnancy and whether dietary management will be more effective if initiated before attempting a pregnancy.
- o Lysosomal storage disease.
- o Experimental therapies in enzyme replacement.
- o Reproduction in the mentally retarded.
- o Natural history of genetic diseases associated with mental retardation and principles of medical management.

Staff Review

The genetic and cytogenetic aspects of MRDD and inborn errors of metabolism have been primary research emphasis areas for the MRDD Branch since its inception. This emphasis is expected to continue.

Research advances in this area are rapid. For this reason, the Branch has not waited upon completion of its planning effort to implement a cooperative study to evaluate the safety and efficacy of chorionic villi sampling (CVS) as a technique for prenatal diagnosis. This study is now in progress.

It should be noted here that large numbers of mentally retarded children, mostly with Down syndrome, have traveled to West Germany for "cell therapy." Staff review of this treatment has found little scientific justification. In addition, there is now the danger the injected cells, drawn from fetal tissues, may carry a slow acting virus. Because large numbers of children have received and will receive this treatment, watchful surveillance has been advised.

Action Steps

- o Convene a workshop on the molecular biology of mental retardation.
- o Issue an RFA on gene therapy using in vitro systems and animal models.
- o Issue an RFP on the development of less invasive prenatal diagnostic methods early in pregnancy.
- o Convene a workshop on the biochemical control of differentiation.
- o Issue an RFA calling for applications concerned with experimental therapies on enzyme replacement.
- o Maintain surveillance of cell therapy for the possibility of slow virus infections.
- o Continue routine staff programming highlighting the priority areas noted in this section of the Research Plan.

V. NUTRITION, TERATOLOGY, AND DEVELOPMENTAL PHARMACOLOGY

Section IV has addressed the disturbances that result from inherited diseases. This section discusses those that result from nutritional inadequacies--specifically protein deficiency--and those that result from exposure to toxic substances either preconception, in utero or postnatally. These issues involve the disciplines of nutrition, teratology, and developmental pharmacology. The perspectives of each of these three disciplines on mental retardation and developmental disabilities and needed research in those disciplines are reviewed in turn.

Current Knowledge and Next Steps: Nutrition

Protein malnutrition is clearly associated with negative effects on the developing central nervous system (CNS). Subnormal CNS development, in turn, is associated with mental retardation and developmental disabilities. The crucial issues are what is the detailed pattern by which this association occurs, and to what extent is such damage reversible.

It is generally understood that malnutrition and undernutrition in humans is associated with lack of sanitation, infectious diseases, low socioeconomic status, social and psychological stresses, and the like. As a result, retrospective and prospective studies in humans are confounded by many variables, making it difficult to ascertain the role of nutrition itself on the developing young. It is even very difficult to carry out rigidly controlled clinical studies on the effects of food supplementation on early development, as the inability so far to demonstrate a beneficial effect of protein supplementation makes clear. Several possible reasons for the failures have been cited in the literature and serve to illustrate the difficulties encountered by such clinical trials with human subjects. These experiences strongly indicate the need for animal models.

Research using the albino rat has produced extremely provocative results which should now lead to further research on the issue of protein malnutrition. The rat is a good model for such research because the stages of development of the CNS in the rat have clearly analogous stages in CNS development in the human. In particular, in the rat prenatal influences affect the CNS before the "brain growth spurt," postnatal (lactational) influences affect it during the brain growth spurt. In the human, these two stages occur in the first and second trimesters of gestation, and the third trimester, respectively.

When mild protein malnutrition was instituted during the prenatal period, marked central and peripheral chemical changes were demonstrable at birth, i.e., before the brain growth spurt. These changes were not reversible by the institution of a normal protein level during lactation. When mild protein malnutrition was administered during lactation (i.e., during the brain growth spurt) to rats that had been well-nourished during the prenatal period, similar central chemical changes occurred. In contrast to the changes due to prenatal malnourishment, however, these changes could be reversed by dietary rehabilitation.

It should be noted here that these two types of protein malnutrition could not be distinguished postnatally either from each other or from rats with normal CNS function on the basis of either body and brain weight at birth or the physical growth curve. Thus, these typical markers proved insufficient to

predict risk of irreversible brain damage, at least in the rat. Further research, however, demonstrated that the irreversibly CNS-damaged rats could be distinguished both from those with reversible damage and from normal rats by their non-esterified fatty acid (NEFA) level. Thus, in the rat, plasma levels of NEFA can differentiate between pre- and postnatal protein malnutrition and between irreversible and reversible changes.

Intergenerational effects of prenatal malnutrition in females on brain underdevelopment and learning deficits have also been demonstrated in the rat, even in the absence of postnatal malnutrition, and with normally nourished male mates. Further, one generation of nutritional rehabilitation was not sufficient to offset two generations of malnutrition. Finally, in the specific case of protein malnourishment, it has been demonstrated that a mildly deficient protein diet, if repeated for two generations of mothers, produces the effects (one of which is small-for-gestational age offspring) of a severely deficient protein diet in the second generation.

Current Knowledge and Next Steps: Teratology

Teratology is that division of embryology, pathology and clinical medicine which deals with exogenously produced abnormal development and congenital malformations. The branch of teratology most relevant to MRDD deals with the effects of prenatal damage. In the past, teratologists have typically pursued research into the effects of prenatal damage by examining the unborn and newborn for structural abnormalities. Many such abnormalities have been discovered and their etiologies established.

Since the early 1970s, however, there has been a growing awareness among clinicians and basic scientists in the area that many forms of damage to the embryo and fetus have not been detectable through structural abnormalities but rather through detailed examination of the functional integrity of the organism. It has been demonstrated unequivocally in animals that agents capable of producing structural malformations of the CNS at high doses, would reliably induce behavioral abnormalities at lower, nonmalforming, doses. This concept led to the development of a subspecialty ultimately designated behavioral teratology. Behavioral teratology now appears to be one of the most promising areas of teratology for the further elucidation of MRDD, although possibly one of the most frustrating as well because of the difficulty of developing analytic approaches to the causes of processes as complex as specific behaviors.

There is substantial evidence, for example, that behavioral abnormalities appear in humans as they develop who were judged, as apparently normal at birth using standard assessment procedures. It is now clear that more refined assessment procedures--monitoring sleep/wake states, for example--can identify infants who in fact have subtle neurological damage that leads to serious dysfunction at a later age before any manifestation of behavioral dysfunction.

There is also evidence, from rat research, that behavioral and physiologic (nongenetic) mechanisms can communicate risk factors for behavioral disturbances across at least two generations. One example concerned the effects on their offspring of removing female babies from the nest box briefly and then replacing them (called handling). The conclusion of the research, which controlled for genetic influences, was that stimulating the

females in their own infancy brought about a set of physiologic changes on their children that expressed itself during the prenatal period and also brought about a set of behavioral changes expressing themselves during the postnatal period. Followup research ascertained that similar effects were still apparent in the grandchildren of the original females (the mothers of whom had been raised under the same conditions as the control mothers).

The formidable challenge is to be able to identify and separate out the influences on development that are traceable to prenatal experiences (drug intake, prepregnancy experience of the mothers, etc.) from influences that are due to the effect of the postnatal environment on the developing infant. Only in this way can we hope to disentangle the complexities of development, including the interaction of biological and environmental factors as an ongoing process.

Progress in this area requires observation of human infants and of animal models. Even though it is now possible, under certain conditions, to predict general developmental risk status of apparently healthy infants, it is not possible to intervene experimentally to seek out the neurological and physiological mechanisms responsible. In addition, there are other risk factors in the human for which there are not as yet effective prediction procedures. Thus, knowledge of developmental processes needs a blend of investigative studies on human infants and experimental studies with animal models of human developmental processes (either normal or abnormal). Certain principles should be followed in the selection of animal models for developmental research. First, the animal model in question should appear to have an analogous or homologous process to the one being investigated. Second, a procedure to measure this process must be possible with the animal model that parallels the one used with humans. Physical growth, sleep/wake states, or infant/mother interactions all satisfy these criteria (although physical growth has been found less than ideal in rats because normal physical growth can be accompanied by CNS damage). Third, the changes in performance of the young animal over its developmental time span must parallel those found for the human. For example, the gestation and lactation periods of the rat, as noted, have appropriate human counterparts.

It has long been stated that the vast majority of all cases of mental retardation are of nonorganic origin. It has often been similarly assumed that other developmental psychological disabilities, be they intellectual, emotional, or psychosocial, are similarly and primarily not organically based. It still appears that many cases of mental retardation and developmental disabilities are of psychosocial origin; however, it may be appropriate now to question the assumption that this represents the overwhelming majority of causes for cases that remain unexplained. If there is one thing that the last 13-15 years of research in teratology has shown, it is that there are a number of potentially identifiable causes of mental retardation and developmental disabilities still to be discovered, many of which are in the chemical environment. While it is not possible to estimate the contribution of chemical versus other causes to CNS dysfunction, it is safe to say that intensified research into these areas holds out the prospect for identification and perhaps eventual prevention of a significant fraction of those cases currently labelled as of 'unknown origin.' A brief review of some recent major advances helps to illustrate the point.

Fetal Alcohol Syndrome. A major impetus to behavioral teratology arose from the clinical discovery of several new developmental disabilities of prenatal origin in which CNS dysfunction was the most serious effect. Foremost among these was the unraveling of the cluster of signs and symptoms termed the fetal alcohol syndrome (FAS). The manifestations of this disorder include minor facial dysmorphology, growth retardation, increased incidence of major malformations and intellectual and other behavioral defects. Alcohol-related behavioral effects, such as impairment in central processing of information, have been identified as early as one to two days of life which persist at four years of age, suggesting long-term consequences of in utero alcohol exposure.

The reason for the behavioral and anatomical abnormalities accompanying FAS is not known. Determination of the teratogenic effect of ethanol and/or acetaldehyde is confounded by some degree of undernutrition among alcoholic women. Nonetheless, available data suggest that malnutrition is not solely responsible for FAS, but that reduced protein synthesis results in restriction of cellular proliferation and differentiation at critical periods of development.

Although the full implications of FAS are still not completely understood, the public health implications of the condition are considerable. A sizable number of fetuses are potentially at risk to alcohol exposure in utero. The prevalence of severe, chronic alcoholism during pregnancy has been estimated to be between 0.42 to 1.25 per 1,000 pregnancies. It is clear that if alcohol can produce FAS at high doses, then, at lower doses, partial expressions of the disorder may reasonably be expected. Since a much larger percentage of the population consume lower doses of alcohol than are represented by the FAS child's mother, the risk of embryopathy may be even more widespread.

Anticonvulsants. Another newly recognized clinical disorder in newborns, having considerable overlap with the story of FAS, has been the description of the fetal hydantoin syndrome, fetal trimethadione syndrome, fetal valproate syndrome, and fetal barbiturate syndromes. These related disorders all exhibit mental deficiency as their major handicapping outcome. Although some debate continues over the risks of developmental disorders in children from epilepsy versus antiepileptic drug therapy, or even the combination of these, most of the evidence points to significantly increased risks to those infants born to epileptics on anticonvulsants during pregnancy.

Narcotics. Along with these newly recognized drug-induced prenatal causes of mental retardation, continued research on the effects of narcotics has documented, in both humans and animals, the psychological consequences of prenatal narcotic exposure. The short-term consequences of the narcotics have been recognized for many years, but the newer research of the 1970s and early 1980s has shown that these children are at increased risk for more subtle long-term behavioral problems, particularly in the areas of attention deficits and emotional lability, factors which may contribute to developmental learning disabilities.

Exposure to Environmental Hazards and Hazards in the Work Place. The behavioral teratogenic effects of drugs represents but one direction in this new field. The effects of environmental hazards, including in the work place are also important areas for research. For example, it has been a recognized theoretical possibility for some time that if maternal exposure to harmful

agents can damage the egg or embryo, then paternal exposure could damage the sperm prior to conception. This very early form of damage could alter the subsequent development of the CNS, leading to behavioral dysfunction in the offspring. This theoretical effect has now been demonstrated in laboratory tests, so far only in animals. The implications of this discovery for the identification of causes of prenatal behavioral dysfunction could be profound because of the occupational exposure of many men in the work force to chemicals of unknown male-mediated behavioral teratogenic potential.

Direct Postnatal Damage from Lead. One reason that the developing brain is perhaps the primary organ system that should be targeted for research within the area of functional teratology is because of its central and irreplaceable role in the quality of human life and because of its protracted and complex development. These characteristics suggest that the CNS may have an exaggerated susceptibility to damaging influences compared to other organ systems. Although most current information derived from animal research points to the idea that organogenesis represents the period of embryonic development when the CNS, as with all organ systems, is most sensitive to a damaging influence, one of the unique aspects of the CNS is that it continues to develop and therefore continues to be sensitive to some types of damage during fetogenesis and even postnatally. An area of research where postnatal brain damage has been recognized for some time is lead encephalopathy. Despite the fact that this problem has been identified and studied in children for years, research on the more subtle behavioral consequences of lead exposure remains a complex problem which is difficult to pin down. Yet new data show that 2 percent of all white children in the U.S. and a staggering 12.2 percent of all black children between 6 months and 5 years of age have blood lead levels above 30 ug, a level used to trigger referral for treatment by Centers for Disease Control standards. The percentages are even higher for urban children, and higher still for urban, lower socioeconomic level children.

Current Knowledge and Next Steps: Developmental Pharmacology

Developmental pharmacology is the study of (1) medications used extensively or primarily in developmentally disabled populations, and (2) the effect of drugs on human development more generally.

Developmental pharmacologists have spent substantial effort and made considerable progress in the first area. Important subjects still in need of research in the area of medications include the behavioral effects of psychopharmacological drugs used in mentally retarded individuals, about which there is considerable controversy, and the effects of drugs on developmentally disabled individuals who are mentally retarded and have psychiatric problems. At this time, however, the major emphasis in the field is shifting to the second area--the effect of drugs on human development more generally. This means, almost by definition, examination of pharmacologic effects earlier and earlier in the process of human conception and development.

Because of this trend, the interests of teratologists and developmental pharmacologists are overlapping to an ever increasing degree, with recent developments in both fields likely to improve our understanding of interacting processes which affect both physical and mental development. On the one hand, teratology, after years of screening for embryotoxic compounds, is now becoming more involved with mechanisms of birth defects.

Cytotoxic mechanisms described in tissue culture are beginning to be examined in situ and the importance of genetic control of cellular responses to environmental agents is being stressed. On the other hand, developmental pharmacology, long at a loss for discernible endpoints of drug action, has recently been provided with much improved access to developing organisms. Cell and organ culture, in vitro fertilization, embryo explants, and improved methods of chemical and physiologic measurement, including noninvasive visualization of the human conceptus by ultrasound, offer exciting opportunities to investigate pharmacologic responses during development.

It is clear that the basic principles of drug action--dose distribution, drug-receptor interactions, and receptor-effector relationships--are all relevant during gestation. The challenge for the pharmacologist, then, is to apply classical approaches to the study of drug action in the context of new understanding of embryonic and fetal physiology.

A large number of drugs and environmental agents have been classified as potentially embryotoxic to humans based on their actions in in vitro systems. Many are also teratogenic in animals when administered in high doses. It is now time to assess their risks during human development, their distribution, metabolism, and relative toxicity in both maternal and embryonic tissues. Dose-response curves need to be defined and their variability across species determined. Models need to be developed which can distinguish embryonic from maternal effects. Methods need to be developed which can associate phenotype with toxicity, particularly in humans.

But developmental pharmacology should not be concerned solely with toxicity of xenobiotics. New diagnostic and monitoring techniques now provide unprecedented access to the human fetus and the possibility of fetal therapy. Deteriorating cardiac function and suspected inborn errors of metabolism have already been approached, but these efforts have been primarily on a trial and error basis. With ultrasound, one can follow growth and development of the brain and, together with other methods of fetal monitoring, diagnose viral infections, hemorrhage and hydrocephalus. In order to approach these and other problems in utero much more information about transplacental pharmacokinetics and pharmacodynamics will be necessary.

Finally, since drugs are developed primarily for use in diseases affecting adults, few have been studied from the standpoint of growth. Growth disturbances are frequently associated with mental dysfunction and developmental delay. Numerous therapeutic agents have been implicated as affecting intrauterine growth. Hormones and psychoactive agents may alter postnatal growth. The extent to which mental dysfunction reflects more global effects of xenobiotics on general growth processes is currently unknown.

Conclusions and Recommendations

The fields of nutrition, teratology, and developmental pharmacology all have major and increasingly overlapping roles to play in identifying the etiology and ways of preventing or ameliorating mental retardation and developmental disabilities.

Methodological research should be an area of major research effort. It should include development of markers that can be used clinically in newborn and developing infants to identify risk factors, pre- and postnatal. If such

markers are found, it may be possible to pursue the hypothesis that first and second trimester stressors can cause CNS damage that is irreversible, but that third trimester stressors produce damage that is reversible. Methodological research should also include development of chemical and behavioral assessment procedures that can be applied at birth, can be continued into adulthood in essentially the same form, have known CNS correlates, and have cross-species generality.

There are at least three reasons for emphasizing the need for methodological research at this time. (1) The discovery of new forms of behavioral teratogenesis and the detection of known types at lower exposure levels will be determined by the development of ever more sensitive tests of CNS functional integrity. This is true whether the research is on animals or directly on children and infants. A major issue related to this is the growing need for long-term follow-up data, particularly in humans, who have had documented exposure to potentially harmful agents prior to birth or during early postnatal life. (2) More specific and more powerful methods will greatly advance our ability to meaningfully relate CNS dysfunction to its underlying pathophysiological basis. Ultimately, this latter area will probably do more than any other to enable us to thoroughly understand and prevent behavioral teratogenesis from occurring, whether it be from nutritional, toxic substance, or other cause. (3) If regulatory authorities move ahead with guidelines for screening all new drugs and food additives, and many other agents for behavioral teratogenesis, then the value of these safety assessment procedures will clearly hinge on the adequacy of the methods used to test for it.

Research also is needed applying the new techniques of molecular biology to mammalian embryology. Techniques used to study molecular and cell biology should be adapted for investigation of developmental processes in the CNS. The need for more information about early human gestation is crucial. Clinical experience with in vitro fertilization in humans underscores the fact that not enough is known about early human gestation, as does our nearly complete ignorance about the process of spontaneous abortion. Most human reproductive pathology occurs within the first few weeks of gestation, yet, to date, only cytogenetic abnormalities have been systematically studied in spontaneously aborted tissues. Further characterization of the biochemistry of abortuses with normal karyotypes could provide interesting and useful information about the reasons for pregnancy losses. Spontaneously aborted tissues could also be cultured and used as an experimental system in which to examine genetically controlled responses to toxic agents.

Further investigation of paternal effects on development is also important, as evidence that the environment also influences reproductive function in males becomes increasingly clear. Infertility seems an obvious consequence of toxic exposures in men, but abnormalities of semen or sperm may also affect postconceptional processes. Work to date has been preliminary, but paternal administration of drugs and toxins in animals does appear to affect survival of the conceptus. Models using intact animals will clearly be important, but in vitro fertilization and embryo explants may also prove to be very useful.

With respect to developmental pharmacology several priority items stand out. First, agents that have been found toxic in in vitro systems and animals should be assessed for their risks during human development. Second, much

more emphasis needs to be placed on the potential for in utero therapy. In particular researchers need to develop animal models and consider methods of sampling fetal fluids in humans. Third, the effects of drugs on intrauterine and extrauterine growth should be investigated systematically. Fourth, development of in vitro methods of screening for the CNS effects of potential teratogens should be given priority attention. A final point to be made is that epidemiologic studies in the areas of toxicology and developmental pharmacology should have high priority. (See section II for more detail.)

The full implications of FAS are still not completely understood. Investigation of the spectrum of fetal alcohol effects and their associated risk factors (maternal age, parity, nutritional status, infections, etc.) represent areas of major future concern that deserve special attention. Continued research on the influence of variables such as dose, timing, and pattern of alcohol intake and the possible genetic characteristics that may predispose for fetal alcohol damage must not be overlooked.

A better understanding of the delayed effects of abnormal early development is important. Relationships between behavioral abnormalities identified in older children or adults and the prenatal environment need to be carefully examined. A considerable body of animal data indicating that pre- and postnatal insults have long-term behavioral effects emphasizes the need for further investigation. These studies need to be expanded and the mechanisms responsible delineated.

Staff Review

Protein deficiency is a major problem world wide. Much research has been done to elucidate the deleterious consequences of this deficiency. Priority should now be given to examining intergenerational effects.

Relative to the biologic measures, research into behavioral measures--particularly those concerned with higher order mental functions (intelligence) and social behavior--appear modest. Strengthening and expanding the tools and methods used in behavioral teratology for study of these issues is needed.

Branch investment in the areas of teratology and behavioral pharmacology is relatively small. Its concern and interest for them is large, however, and fortunately shared by others inside and outside the NICHD. Inside the NICHD, the Genetics and Teratology Branch, CRMC, is heavily involved. Other Federal agencies with overlapping interests in these areas are the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) and the National Institute of Environmental Health Sciences (NIEHS), NIH. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) of ADAMHA supports research on alcohol relevant to MRDD Branch concerns, and the NIEHS supports research on the effects of environmental teratogens on development. Branch staff maintain a cooperative liaison with the Genetics and Teratology Branch of the NICHD and with these agencies in order to assure support and progress in these fields.

Action Steps

- o Issue an RFA calling for applications employing interdisciplinary research on intergenerational effects (see also section VIII).

- o Support a program project to investigate intergenerational effects using an appropriate animal model.
- o Convene a conference on behavioral teratology (see also section II).
- o Fostering the other research recommendations through continuing cooperative liaison with the NIAAA and NIEHS.

VI. OBSTETRICS AND PERINATOLOGY

This chapter is concerned with the relationship between mental retardation and brain damage in utero, during labor and delivery, and perinatally.

We divide our discussion into three subsections: pregnancy, the intrapartum period, and the perinatal period. Genetic factors are only alluded to in passing (they are treated in detail, along with prenatal diagnosis, in Section IV). The same is true of nutritional, teratological, and pharmacological factors in the mother's experience either before or during pregnancy (treated in detail in Sections VI and XIII).

It should be emphasized at the outset that the major message of the section is that few areas in medicine have changed as rapidly as those of obstetrics and neonatology. Because of these changes intrapartum physical trauma as a cause of brain damage has largely been eliminated. As a consequence, somewhat paradoxically, we are left with a host of new set of unanswered questions about the causes of brain damage.

Current Knowledge and Priority Areas for Further Research

Pregnancy. Advances in our ability to identify women at high risk for an abnormal pregnancy, as well as in our ability to identify the abnormal or high-risk fetus, have been dramatic. Prematurity and low birth weight are the two fetal factors highly correlated with adverse neurological outcome. Changing concepts of maternal nutrition and weight gain have had, and can have further impact on increasing fetal weight. New understanding of alterations in maternal blood volume and its effects on placental flow, as well as the effects of work, stress, and fatigue on fetal size and prematurity also have implications for management of the maternal-fetal unit that may improve outcomes. Many factors associated with lifestyle can be altered, and specific pregnancies monitored. The decreased rate of preterm births in obstetric units using these and similar approaches is impressive.

The changing approach to fetal surveillance using amniocentesis, ultrasound, fetal monitoring, and in the future, nuclear magnetic resonance, also will allow better identification of malformations and more careful monitoring of fetal somatic and head growth (see Section IV for detail). In addition, these techniques offer the potential for medical or surgical intervention in specific problems and coupling these techniques with assessment of fetal well-being could provide evidence of stress in the fetal-maternal unit and lead to intervention and prevention of damage. Assessment of the duration of intrauterine problems may be as important as their detection.

Vaccination has decreased maternal rubella and its devastating effects on the fetus. Vaccines to prevent other intrauterine infections, as well as infections of the newborn, such as herpes, streptococcal meningitis and H. influenza, could further decrease mortality and morbidity. With all these advances, however, we still cannot identify the majority of the brain-damaged population prospectively, nor the etiology of many of them retrospectively. Race, socioeconomic factors, lifestyles, pre- and postnatal environmental factors, education, and relationships with family, school and peers, all cluster, interact, and influence function and adaptability in a way that we cannot currently disentangle. And in the area of mental retardation, we cannot disentangle the individual environmental

factors that interact with the individual child's biologic potential to produce a given level of function.

As noted in Section III, development of the central nervous system is a complex series of contemporaneous and interactive events. Synaptic interconnections form the circuitry of the nervous system, which is then modified by programmed cell death and process elimination. Those events, which form the basis for later function, must be influenced by local factors within the developing nervous system and general factors of nutrition of the developing fetus and his environment, as well as by factors affecting the health and environment of the mother. The effects of these multiple factors are further modified by the genetic endowment of the fetus. Minor (or major) abnormalities at any stage in the developmental process will have continuing and interacting effects on further development. The plasticity of the infant's nervous system, which may modify these alterations in development, later may compensate for defects throughout pre- and postnatal development. Our lack of information about factors that induce, regulate, and modify development and repair presently make it virtually impossible to ascribe developmental abnormalities to any single event, or to predict the consequences of any abnormality or event that occurs during development.

The Intrapartum Period. The concept of birth trauma as a significant cause of neonatal mortality and brain damage was well established in the 1800s and early 1900s. Prolonged and difficult labor threatened mothers as well as infants. These observations led midwives and obstetricians to attempt intrauterine manipulations and eventually led to the use of forceps. The physical trauma of these interventions at times resulted in damage to the infants' intracranial contents and led to the concept of obstetrically induced trauma. Use of forceps prevented some intrapartum deaths and damage, but it caused others. Today, high forceps are no longer used and mid-forceps are used rarely. Cesarean birth has largely replaced these potentially traumatic forms of delivery, and physical obstetric trauma as a cause of "brain damage" is now rare.

As physical trauma has become rare, the role of asphyxia and its biochemical concomitants has become more apparent as a cause of cerebral palsy and of the mental retardation accompanying cerebral palsy. But, major challenges now lie in the early detection and quantification of the degree and duration of asphyxia and in its prevention. Low Apgar scores have been shown to be related to subsequent neurologic deficit, but are also influenced by gestational age and other disease states. Only when the Apgar score is low (< 3) for a long time (more than 10-15 minutes) is there a high risk of cerebral palsy and mental retardation. Even in these infants, one-half have no neurologic residua. Perhaps it is the duration of the intrapartum asphyxia, not its presence just prior to delivery, that determines the significance of the asphyxia. Perhaps the substrate upon which asphyxia is superimposed is crucial--the growth deprived, small-for-gestational age infant who has less tolerance of additional insult. The Apgar score is presently only an indicator that asphyxia has previously occurred. Prevention of neurological damage requires early identification of the asphyxiated infant prior to or during labor, and of the severity and duration of the intrauterine asphyxia.

The presence of early and heavy meconium staining of the amniotic fluid appears to be one indicator of previous fetal distress. Electronic fetal monitoring and fetal blood sampling for acidosis provide other indicators. However, each technique measures single points in time rather than duration. While these abnormalities each are associated with increased risk, the dimensions of that risk vary, and the correlation of these abnormalities with other factors predisposing to damage in the fetus remains unclear.

Even if asphyxia were detected early and appropriately treated, "brain damage" would not be eliminated. In the Neurological Collaborative Perinatal Project, 73 percent of children with cerebral palsy had Apgar Scores of 7-10 at 5 minutes. Did they have intrauterine asphyxia or were other factors the cause? We do not know.

Obstetric interventions no longer are viewed as the one common cause of neurological damage. But could obstetric intervention prevent asphyxia and its effects on the brain? We can identify intrapartum factors that increase the risk of neurological damage, yet most infants with these risk factors do well. We need to understand and identify the interplay of risk factors that warrant obstetric intervention.

One of the major factors in decreasing mortality and morbidity has been the advent of nurseries for high-risk infants. The benefit of technology in improving the quantity and quality of survivors is well documented, but attitudes toward the very small, high-risk infant may play a role as well. Underestimating fetal weight (and thus viability) may negatively influence the use of both obstetric and neonatal technology. It has been shown that if the fetus is treated as if it is viable and will survive, outcomes are improved.

The Perinatal Period. There has been a striking decrease in mortality among low-birth-weight infants, and particularly in very-low-birth-weight infants weighing less than 1500 grams. Now, even for infants weighing between 700-800 grams (25-26 weeks gestational age), survival approaches 50 percent, and for infants weighing between 900-1500 grams, survival has improved even more dramatically. This increase in survival has raised concerns about neurologic deficit in the survivors. There has been a decrease in severe motor deficit in these very-low-birth-weight infants which has paralleled the decrease in morbidity. However, even "neurologically normal" very low birthweight infants average infants slightly lower IQs and higher incidence of visual-motor, attention and behavior problems than do full-term infants. The difficulties in designing and evaluating follow-up studies and evaluating changes in care in a timely fashion have resulted in much information but little insight. Clearly we need better methodology to predict outcome early, and better approaches to evaluating the role of various intervention strategies to prevent or ameliorate neurologic deficits.

Among the most common neurologic problems of the preterm infant is subependymal/intraventricular hemorrhage. Despite its frequency, we know little of the source of bleeding, the factors involved in its pathogenesis, or even of the factors associated with its prognosis. These are fertile though frustrating areas of research, and their interplay with hypoxia and

vascular control may be major determinants of both gross and subtle neurologic deficits.

For cerebral palsy alone do we have a major identifiable antecedent: perinatal asphyxia. The effects of this asphyxia vary with its severity and duration, as well as with the gestational age. Thus, we see germinal matrix (and choroid plexus) bleeding in the preterm infant, periventricular leukomalacia in both pre- and full-term infants, and necrotic cortical lesions in the full-term infant. Useful indicators of the severity of the hypoxic insult are the clinical pattern of distress and recovery after significant asphyxia, a low (< 3) 5-minutes-and-later Apgar score in conjunction with meconium staining, time until initiation of spontaneous respiration, and time until return of tone. The early onset of seizures and the infant's level of consciousness are predictors of later deficit.

These early neurologic abnormalities identify the child at high risk for permanent damage. Identifying hypoxia and its clinical effects in the first hours of life would allow intervention in what appears to be a progressive process: hypoxia -->cell damage -->swelling-->vascular compromise -->further hypoxia. If this self-perpetuating mechanism for severe cortical damage is correct, then appropriate intervention could prevent many of the severe effects of hypoxia. Further studies using animal models and the newer imaging techniques to evaluate this pathogenesis, as well as studies to evaluate specific interventions, could lead to treatment of the hypoxic infant and prevention of much severe neurologic damage.

Previous writings on perinatal causes of neurologic dysfunction would have emphasized traumatic injuries and kernicterus. Today, brachial plexus injuries and spinal cord trauma are the only remaining physical traumas that significantly contribute to neurologic dysfunction. The decreased incidence of even these now uncommon traumas is documented.

Conclusions and Recommendations

Epidemiology. Prospective studies of trends in the prevalence of neurodevelopmental disorders, using better definitions of handicap, are needed. Specifically, analysis of cerebral palsy by type and its associated problems, is important. Such information should be correlated with changes in obstetric and neonatal practices and attitudes, in order to ascertain causative relationships. Improved definition and measurement of a suspected risk factor such as perinatal asphyxia, could add great strength to an analysis of the effects of clinical care on developmental outcome. However, such studies of causative factors in neurodevelopmental disorders would be incomplete without consideration of other risk factors besides asphyxia, such as: fetal growth retardation, preterm birth, fetal infections, chromosomal abnormalities, and nongenetic congenital anomalies. These factors are currently thought to outweigh intrapartum asphyxia, at least, as contributors to brain damage.

Obstetrics. The low birth weight infants have a high incidence of breech presentation, prolapsed umbilical cord, third-trimester hemorrhage, fetal distress, and birth asphyxia. It is possible that pressure on the vertex during birth may result in increased intracerebral pressure, subsequent fetal distress, and intracerebral ischemia and/or hemorrhage.

However, this hypothesis is unproved, and the available clinical studies are conflicting in conclusions. Thus, there is an urgent need for prospective, randomized, controlled clinical studies--using birth route as an independent variable--of obstetric variables influencing outcomes for infants of very low birth weight (< 1500 grams).

Intrapartum fetal distress can be identified with electronic monitoring and fetal scalp blood sampling. However, these techniques are limited in detecting intracerebral changes that may lead to ischemia or hemorrhage. Newer imaging techniques, such as positron emission tomography (PET) scanning, and magnetic resonance imaging (MRI), should be evaluated for their ability to distinguish the forms of fetal distress that are neurologically threatening.

Studies of the role of prenatal care on neurological outcome of the child and the effects of maternal work and environment on outcome are needed. Also, the potential of pre-pregnancy planning and genetic and life style counseling to reduce perinatal complications should be evaluated.

Perinatology. Although the problems of respiratory immaturity have become better understood and treated, diagnosis and management of neurologic immaturity have not progressed as rapidly.

Neonatal seizures are thought to reflect asphyxial damage and are considered a marker of later impairment. However, the mechanisms by which seizures themselves produce further damage are poorly understood. Thus, understandably, managements are based on inadequately knowledge, and the effects of suggested treatments are inadequately evaluated. Research directed at these deficiencies is needed.

Cerebral vascular control may play a major role in the occurrence of intraventricular hemorrhage and its consequences, although we do not know how. Thus, techniques involving Doppler flowmetry or the approaches to improve the measurement of cerebral blood flow could elucidate the pathophysiology involved with intraventricular hemorrhage. How seizures themselves produce further damage is poorly understood. Thus, understandably, managements are based on inadequate knowledge, and the effects of suggested treatments are inadequately evaluated. Research directed at these deficiencies is needed.

Staff Review

Research in obstetrics and perinatology within the NICHD is concentrated in the Pregnancy and Perinatology Branch. The MRDD Branch also has major holdings in these areas. Preterm births and low birth weight infants are a major concern for the MRDD Branch. These biologically vulnerable infants are the subjects of intensive study under the rubric of early identification and early intervention programming (see Section XI). The methods and outcomes of care provided these infants in neonatal intensive care units (NICU) is also a matter of strong research interest.

Socioeconomic and life style issues also need to be addressed to complement the biological and medical research accomplished in obstetrics and perinatology (see Section XIII).

Action Steps

- o Encourage applications concerned with the effects of life styles on pregnancy outcomes, on the fetal alcohol syndrome, and the use of drugs.
- o Work with the Pregnancy and Perinatology Branch of the NICHD to develop research applications on prenatal and perinatal factors related to brain disorders with particular reference to mental retardation.

VII. PSYCHOBIOLOGICAL PROCESSES

Psychobiology refers to the interface between biology and the study of behavior. Discoveries in genetics, neuroscience, and experimental psychology during the last generation form the basis of modern psychobiological science, which covers the subareas of behavioral genetics, behavioral embryology and teratology, developmental neuroscience, developmental psychophysiology, and developmental psychopharmacology. New concepts, methods, and technologies in the developmental sciences related to behavior are most important for the study of mental retardation. Many forms of mental retardation are the outcomes of maldevelopment of the nervous system. These developmental abnormalities may be brought about by genetic and environmental factors operating in combination to alter normal differentiation, growth, and maturation of neurons and synaptic connections. This section begins by discussing what the constituent subareas have in common. It then reviews each subarea briefly, in turn.

Methodological Approach

All the subareas of psychobiology have methodological approaches that are similar in important respects. First, they are interdisciplinary, requiring training in behavioral and biological concepts. Second, they take advantage of complex modern technology. For instance, the CAT scan and ultrasound have had a major impact on early identification of infant behavioral pathologies. Behavioral and psychophysiological techniques for segmenting information flow through the nervous system (e.g., computer-averaged evoked potentials, positron emission tomography, regional cerebral blood flow, and most recently magnetic resonance imaging (MRI)) have fostered impressive gains in analyzing CNS.

Third, all the subareas of developmental psychobiology routinely use longitudinal research designs or observe changes in development at different levels of maturation. Because follow-up studies with humans are not always feasible because of their cost, well-chosen animal models are also used to study important analyses of sequences in development. As will be discussed further below, studies employing nonhuman primates and other animal models in ecologically valid contexts seem most important for mental retardation research at this time.

Fourth, all the subareas of developmental psychobiology are working to redefine what constitutes the most relevant behavioral unit. High speed photography, movement notation, and computer simulation preserve and analyze precise sequences and interactions of body parts. Psychophysiolgists are proposing complex quantitative techniques to derive response variables that are accurate reflections of underlying neurophysiological regulation. These approaches promise breakthroughs in the descriptive analyses of normal and abnormal behavior.

Finally, many look for causal links by starting with normative baseline information and then systematically attempting to vary internal or external factors that may be making an essential contribution to normal development. A particular factor is taken away, precluded, or substituted for (e.g., hormone, movement, sensory experience, enzyme) to see if the usual behavior outcome becomes pathological or abnormal. In such a way, psychobiology can come to

grips with the essential ingredients of normal developmental processes and, thus, suggest possible remediation in the cases when development goes awry.

Current Research and Next Steps in Behavioral Genetics

The search for genetic behavioral disorders is proceeding rapidly--with new data every week on fragile X mental retardation, Tourette's syndrome, endocrine disorders, and the like. Many forms of disorder that have a roughly Mendelian or usual chromosomal pattern will be discovered, and with the help of careful behavioral analysis, more will be known about special forms of these disorders in the next decade.

Progress is also being made in conceptualizing the ways in which normal genetic variation influences what kinds of experiences people have in their environments. This will be fostered by quantitative genetic strategies. Designs using contemporaneous relationships such as twins and non-twin siblings are particularly useful in disentangling genetic and environmental components of variation. Adoption designs provide the most powerful tool for accomplishing this goal, as well as for studying specific environmental influences free of genetic confound and exploring genotype-environment interaction and correlation.

In addition to estimating the extent to which developmental disorders are genetic in origin, these same methodologies provide important information concerning environmental influences. For example, despite the current trend towards emphasizing genetic aspects of psychopathology, behavioral genetics provides some of the best evidence for substantial environmental variation. Most importantly, these studies show that the critical environmental factors--whatever they might be--are not shared by children in the same family; they operate in such a way as to make two children in the same family as different from one another as are children in different families. Because it is usually assumed that the relevant environmental factors depend on family experiences, individual experiences within a family have rarely been studied. We need to begin to identify environmental factors that make children in a family different from one another. To do this requires studying more than one child per family.

A most important point to emphasize concerning developmental behavioral genetics is that it provides tools to explore genetic sources of developmental change as well as continuity. Such exploration may reveal the key to understanding the instability that is predominant in most realms of child development.

As noted in section V on Nutrition, Teratology, and Developmental Pharmacology, nongenetic intergenerational effects on reproductive outcome, growth, and behavior are established facts in rodents. Effects of prenatal handling and other stressors such as high or low temperature on reduced litter size, birth weight, and postnatal growth rate have been established. Effects are also seen in emotionality and avoidance learning. Subsequent generations from stressed 'grandmothers' show measurable differences compared with nonstressed lines, even though these females are not themselves stressed. The presumed mechanism for these effects is altered pituitary-hypothalamic-adrenal functioning in the original fetuses of stressed grandmothers, resulting in intrauterine growth failure. Drug and poison effects on both male and female

rodent breeders also produce intergenerational defects, possibly through chromosomal damage.

In humans, DES (diethylstilbestrol) has recently been shown to produce increased reproductive risk and risk for cancer in the offspring of females whose mothers took this substance. This effect on the grandchildren resembles some intergenerational drug effects in rodents. Although direct experimental data are lacking, epidemiological studies suggest a strong intergenerational effect of social class on low birthweight rates, and possibly some CNS defects.

A tenable, though essentially untested hypothesis, is that 'familial' retardation and other intellectual-learning disorders of unknown etiology have nongenetic intergenerational effects as important causal factors. Without controlled experimental longitudinal studies, it is not possible to distinguish such effects from genetic causes or from postnatal environmental factors. The eventual identification of specific nongenetic intergenerational influences and estimation of the magnitude and generational duration of their effects will require a major interdisciplinary research effort. This will involve basic animal model studies of reproduction, physiology, and behavior--leading to testable hypotheses in human populations involving biomedical, epidemiological, sociological, and psychological parameters.

Current Research and Next Steps in Behavioral Embryology and Teratology

Relationships between prenatal maturation and postnatal development are probably the least understood topic in the study of human behavior. However, work with mammalian species has shown that virtually every major brain and endocrine system--with the possible exception of the latest developing layers of the cerebellum--are formed, connected and mostly functional, by birth or shortly after. Recent studies with rodents suggest that maturation rate and actual structure in parts of the prenatal brain can be strongly affected by the fetal hormone environment. Studies of drug and poison effects, conducted on pregnant females and on sires receiving preconception administrations, show increased fetal mortality, birth defects in liveborns, and deviant postnatal development on many dimensions of behavior. In psychology, a failure to identify postnatal factors resulting in cases of deviant development is almost invariably interpreted as a genetic effect; yet in many instances prenatal etiologies may be responsible. (A theoretical exception to this lack of study is the topic of stress during pregnancy. However, although most medical workers and many students of behavioral development believe that prenatal stress has detrimental effects on human development, the evidence is circumstantial at best.)

Another area about which much more needs to be known is prenatal brain growth. Unlike in rodents, the major events in the structural ontogeny of the human brain occur prenatally. Thus, it is important to understand the timing, cellular interactions, and schedule of synaptogenesis for all major neural systems as they unfold largely before birth. Early childhood is the most significant period of an individual's life, setting the stage for what will unfold at maturity. Thousands of studies exist on behavioral development of children; probably an equally large number of studies report on the changes in one or another biochemical or pharmacological parameter during maturation, such studies mainly being conducted with rodents. But research has also shown that the primate brain is sufficiently different from the rodent brain to

warrant direct study. Elegant studies with both basic science and clinical significance have been performed on the visual system of nonhuman primates. What is now needed is a major effort to support interdisciplinary studies of nonhuman primates that would bridge the gap between biochemical and physiological studies in small animals and behavioral studies in humans.

Recent studies in Israel have made it clear that the surest sign of an unhealthy fetus is one whose movement (activity) is diminished. In the area of human behavioral embryology, as noninvasive electronic monitoring is now possible, normative studies should begin of fetal motor activity and sensory reactivity throughout gestation. Since amount (and kind) of activity must vary over the course of gestation, such descriptive norms would be most desirable. Among the sensory modalities, the auditory one should come in for particular prenatal and early postnatal study now that it is becoming clearer that the maternal voice is very likely experienced by the fetus and shows carry-over effects into the early neonatal period. This approach has ramifications of the highest import for maternal-infant bonding, and the development of speech perception and language learning in human infants.

Current Research and Next Steps in Developmental Neuroscience

Some developmental disabilities, as well as disorders of aging, may involve deficits in basic information storage mechanisms in the brain (see Section III for extended discussion). Research is accumulating which suggests that processes which subserve developmental information storage (e.g., early experience effects) may also be involved in adult learning and memory. We are beginning to close in on probable structural substrates of brain information storage (e.g., synapse formation, molecular basis for addressing axonal growth patterns in the CNS), repair mechanisms of axons in the CNS and the mutual interactions between CNS and the immune system (psychoneuroimmunology). The recent studies on interfacing electric circuits and neural networks will contribute to models of brain information systems. The developments in MRI and PET will yield new information correlating brain blood flow and metabolism with neural dysfunction.

One striking aspect of disorders of behavioral development is their sex linkage. Either androgens (or some other Y-chromosome based product) exacerbate intrinsic tendencies toward disorders or estrogens mitigate them. Real breakthroughs in the area of endocrine modulation of neurobehavioral development are imminent, based upon recent developments in behavioral, physiological, and anatomical research. Research should not be restricted to sex hormones, but emphasize gonadal steroid effects on brain regions and include sex as a variable in animal development studies with other primary purposes. There is some evidence that certain behavioral disorders may involve deficits behavioral functions more generally. Moreover, investigators are urged to in brain lateralization. Until recently, brain asymmetry was thought to be a property found only in the great apes and man. Some evidence, still mixed, now suggests behavioral models of brain asymmetry may be available in lower mammals, and that, as proposed in humans, sex or gonadal hormones may play a role in it. The processes whereby asymmetries arise and the role of genetic sex-linked variables (if any) may be approachable in infraprimate species.

Current Research and Next Steps in Developmental Psychophysiology

Recent research on neural manifestations of cognitive processes such as attention, vigilance, expectancy, and learning strongly suggest that few sensory or motor neural processes are "hard-wired." Rather, these systems continue to be dynamic in adulthood (maturity) and continue to evolve and change as cognitive task variables and other environmental considerations are manipulated. These considerations suggest that basic and clinical research on populations with mental retardation or developmental disabilities using new behavioral and neurobiological techniques may be most fruitful.

The majority of cognitive impairments exhibited by mentally handicapped individuals are often accompanied by a variety of motor impairments. Interest in motor skills research on a variety of variables that mediate performance and the broader theoretical issues that focus on control, coordination, and skill is reflected in the wide range of scientific papers and symposia on motor skills. The increase in activity in motor skills research has been complemented by increased theoretical support and consideration of the idea that perception and action are intimately related. Research on the mentally handicapped is important in this context, not only for determining the influence of traditional learning variables on motor performance, but also on the more important theoretical issues focusing on the nature of control and coordination in those labeled "mentally handicapped."

Technical sophistication in methods of delineating sensorimotor and cognitive abilities has reached the point where significant advances could be made in clinical diagnosis of deficits and in understanding how processing changes with brain maturation. The technique of computer-averaged evoked potentials recorded from the scalp has emerged as a clinically useful neurological procedure in the adult. It may prove even more useful in diagnosing sensory deficits in the infant. Infant visual acuity can be successfully measured, as well as such basic visual system characteristics as the width of spatial frequency channels and the rate of temporal modulation to which the system is sensitive. Measurement of the brainstem response to relatively low intensity acoustic stimulation is also practical. Sensitivity to shorter bandwidths increases in both systems over the first few months of life, and some evidence suggests it may parallel behaviorally measured perceptual capabilities. Mapping the course of such maturational changes in premature and other well-defined groups at risk for learning disabilities offers hope for early detection and treatment of subtle deficits capable of hindering the development of complex skills.

The future of developmental psychophysiology may be characterized by a shift in quantification strategies from the description of physiological responses as unidimensional indices of arousal to the description of specific neurally mediated components. Techniques are being developed which will generate an ensemble of component variables defined by specific neurophysiological relationships. Each specific component variable may behave in a unique though consistent manner. Thus, the application of descriptive statistics to the composite physiological response (e.g., changes in heart rate over time) may obfuscate the sensitivity of the component variables. By decomposing the pattern of easily monitored peripheral physiological responses, important information about central control systems may be derived. Time series statistical methods such as spectral analysis may be very effective in partitioning complex physiological response patterns (such as heart rate) into

component processes that are more sensitive to underlying neurophysiological regulation and, therefore, more sensitive to the cognitive, behavioral, and health variables that developmental psychophysicologists are interested in studying with respect to later development of more complex skills.

Transient, rapid changes in stimulation appear to be important for automatic alerting and initiation of information processing, and they determine many distinctions among speech phonemes. Converging evidence suggests relatively poor ability to detect and use transients at one or more stages of development. Techniques are available, especially through computer utilization, for sophisticated shaping of temporal parameters of stimuli, as in synthetic speech, and for fine-grained analysis of temporal characteristics of response. Such techniques should be exploited to track developing responsiveness of variation in rates of change, spacing, and duration of simple sensory and complex cross-modal stimulation. The knowledge is necessary for adequate design of educational and therapeutic programs, and for identifying aberrant development.

Current Research and Next Steps in Developmental Psychopharmacology

There has been a relative lack of attention devoted to developmental roles of neuromodulatory substances such as endogenous opiates and other neuropeptides. While some work indicates a role in early social development, there has been little examination of effects of manipulation of these systems on brain development or upon more cognitive aspects of behavior.

There is a need for systematic examination of the basic biological and behavioral mechanisms and parameters related to short-term and chronic medication use in mentally retarded populations. Despite carefully controlled analyses with laboratory animals, the degree to which such findings have generality to humans requires further elaboration, particularly with mentally retarded persons. This problem is compounded by the fact that a lack of experimental evidence about the action of specific drugs (absorption, metabolism, half-life, etc.) on children and neurologically different populations calls into question not only dosage requirements but use of the medication at all.

Whereas previous measures of drug effectiveness have included behavioral rating scales or intelligence tests, research has also spawned excellent behavioral assessment instruments. Equally important advances have been the elaboration, within subject and time series, of experimental designs which allow systematic comparison of several drug and/or behavioral interventions at the individual patient level.

Such studies are particularly necessary in light of continuing lack of consensus on which drug treatment is appropriate for a type of problem and a level of functioning. For example, investigators have found mixed results regarding beneficial and adverse effects of psychostimulant drugs with severely and profoundly retarded subjects. Methods are needed for examining in more detail under what conditions this class of drugs, as well as others, can be effective with each type of mentally retarded population.

Little research has been conducted to evaluate the relative effectiveness of behavioral treatments as an alternative to or in combination with chronic medication of mentally retarded populations. For example, a combination of

behavioral and drug treatment may permit medication dosages below levels at which toxic effects occur. The predominant studies attempting such comparisons have been concerned with psychostimulant medications and hyperactive children. The possibility that behavioral interventions could eliminate or reduce the need for medications with more cognitively impaired populations remains open to investigation.

Conclusions and Recommendations

Two major conclusions are to be drawn on the basis of the above discussion about priority research needs in the study of psychobiological processes.

The first is methodological. The focus should be on interdisciplinary research employing longitudinal and cross-maturational designs with well-chosen animal models and the sophisticated new techniques of behavioral and psychophysiological measurement of children.

The second is the focus of the research. As noted elsewhere the mentally retarded fall into two major groups: the severely retarded and the considerably larger group who exhibit mild retardation. Since the latter group are so numerous, since the etiology of a large part of mild retardation is as yet unknown, and since the tools of psychobiology are well equipped to measure fine distinctions at an extremely detailed level, the focus in this area should be on clarifying the causes and consequences of mild mental retardation. Priority subjects for study include:

- o Within-family quantitative behavior genetic analyses that evaluate the contributions of genetics and environment, especially the intergenerational effects of potentially debilitating environments.
- o The prenatal and early postnatal period, especially with respect to development of sensory and motor systems and the effects of stress on development.
- o Central nervous system maturation, especially with reference to endocrine modulation of neurobehavioral processes.
- o Development and disorders of information storage and use.
- o Effects of pharmacological agents on behavior of mentally retarded people.

Staff Review

The recommendation to study intergenerational effects is also strongly made in section V on Nutrition, Teratology, and Developmental Pharmacology. In response, the Branch has already conducted a conference on intergenerational effects. Research evidence is increasingly able to show intergenerational effects of nutrition, drugs, stress, handling and other agents. The mechanisms, other than genetic, for the transmission of intergenerational effects are not well understood. Debilitating intergenerational effects of this type present one possible source for cause of MRDD and expanded studies to explore this issue are needed.

Action Steps

- o Issue an RFA calling for studies on the intergenerational transmission of debilitating effects (see also section V).
- o Issue a Program Announcement calling for research on development of sensory motor systems and the effect of stress on this process during prenatal and early postnatal periods.
- o Give programming emphasis to other recommendations.

VIII. PSYCHOLOGICAL PROCESSES

Most sections in the MRDD research plan address psychological processes in one way or another, in particular section VIII on Psychobiological Processes and section IX on Behavior Analysis. To minimize overlap, the decision has been made to keep this section brief and to restrict the focus to four areas not covered adequately elsewhere: (a) cognition and information processing, (b) perceptual processes, (c) motor development, and (d) affective, motivational, and personality factors.

Current Knowledge and Priority Areas for Future Research

Cognition and Information Processing. The psychometric tradition that dominated psychological research into mental retardation for most of its history has, over the past two decades, yielded to theories and experimental methods designed to identify, isolate, and control component processes associated with learning, memory, attention, problem solving, strategic thought and the like. It is now clear that the most productive research strategy is one that addresses the componential nature of intelligent behavior.

A large amount of information has been accumulated concerning information processing capabilities, and it is known that mentally retarded persons are deficient in many of these when compared to nonretarded persons. What is needed now is systematization of these findings: that is, a complete taxonomy of mental processes and their relationships. Major progress in understanding intelligence and its development depends on successful analysis of interactions among knowledge bases, processing strategies, and metacognition. In addition, it is now clear that intelligence (as an individual difference concept) not only provides a major defining variable for mental retardation but is clearly among the most stable of human psychological traits, as measured psychometrically. That intelligence modulates psychological processes (e.g., smarter people have better memories and learn faster) is partly a theoretical or definitional matter and partly an empirical finding. But the precise manner in which intelligence modulates these processes is not known. Now research is needed to uncover the manner in which psychological processes are mediated by individual differences in intelligence (as well as developmental level, genetic and developmental defects, disease, nutrition, and other factors). Elucidation of this is likely to have two major ramifications. First, it will revolutionize the assessment of mentally retarded persons, leading to development of assessment tools which yield individual patterns of strengths and weaknesses. Second, it will provide important insight for cognitive psychologists in developing theories of mental functioning.

Much information has also accumulated about how mentally retarded individuals perform on tasks of basic cognitive ability. However, very little is known about how these abilities change over time and how they interact. The central concern here is with the continuity of emerging processes that characterize the development of cognition and intelligence. This issue is of obvious importance to any well-developed theory of mental retardation. Whether or not the cognitive abilities which have been studied are stable characteristics of individuals is important to know. There is an implicit assumption that these abilities are relatively constant over time with respect to an individual's rank in the distribution, but this may not be the case. In addition we need

to study processes fundamental to identifying disorders of cognition and behavior associated with specific forms of retardation, learning disabilities, hyperactivity, stereotypic behavior, etc. We separate these as a group as studying them in a developmental framework may or may not be appropriate—it is clearly a matter of scientific strategy that may not be the same for all disorders.

Finally, a great deal is now known about instructional methods with the mentally retarded, including the difficulties that must be taken into consideration (like obtaining transfer). A concerted effort at attempting to convert this knowledge into applied technologies is likely to produce substantial gains, particularly if the findings from mental retardation research are combined with the developing computer technologies to produce computer-assisted instructional materials. Intervention and training studies based on process studies and research strategies that go from basic studies to experimental training studies to intervention per se, also must be considered.

Perceptual Processes. One of the most neglected areas of research in the psychology of mental retardation concerns the role of perceptual processes. Well formalized theories of perception can be found in the generic psychological literature. However, little systematic attention has been directed toward the elucidation of these processes within a coherent theory of intelligence generally and mental retardation specifically. Two elements of perception that warrant greater research support are selective attention and organization, which should include spatial, olfactory, and vestibular systems, as well as visual and auditory modalities.

Motor Development. The majority of cognitive impairments exhibited by mentally handicapped individuals, irrespective of the degree of the handicap, are often accompanied by a variety of motor impairments. In the last ten years, an increased research effort has focused on the inability of mentally handicapped individuals to produce acceptable levels of motor skill performance.

Perception and action are now recognized as being intimately related, and the rather crude separation of cognition activity and motor activity is being reevaluated in a different light. Research on the mentally handicapped, therefore, is important, not only for determining the influence of traditional learning variables on motor performance, but also on the more important theoretical issues that focus on the nature of control and coordination in those labeled mentally handicapped. This is not only intrinsically important from a scientific viewpoint but may have impact on upgrading the quality of life for the mentally handicapped from a vocational and leisure-time perspective.

Affective, Motivational, and Personality Factors. Given the nature of the deficit shared by mentally retarded people, research on personality and motivation in this group can be especially useful to the degree that it helps us understand, and ultimately ameliorate to some degree, performance deficits and their impact. The objective is to (1) identify factors that lead retarded individuals to use their cognitive abilities in less than optimum ways, (2) identify ways of mitigating effects of these factors, thereby improving the

readiness of retarded people to use the abilities they do possess, and (3) understand and enhance the social adaptation of retarded people.

One important area is achievement-related cognition and motivation. Research on school performance and achievement among non-retarded children has generated a rich array of findings on the processes these children use to size up the controllability of various tasks, gauge their own level of competence, and translate these cognitions into various levels of achievement motivation and goal-directed behavior. This research--growing in part out of such traditions as attribution theory, learned helplessness, effectance and mastery motivation, perceived competence, self-efficacy, and the venerable locus of control construct--raises a number of questions that will need to be addressed in concert if we are to understand the behavior of retarded children in school and other achievement-relevant settings: how do retarded children construe the notions of personal competence and ability, and how do they go about assessing their own abilities? What roles, if any, are played by social comparison, feedback from adults (e.g., teachers), feedback from peers, and such structural factors as variations in styles of mainstreaming? How do these and other processes feed into patterns of expectancy and causal attribution for successes and failures in achievement activities? How, in turn, do these cognitions relate to emotional and motivational states and to actual behavior when achievement challenges are confronted? Finally, how do the answers to the preceding questions change over the course of the retarded individual's development?

A second important area is the relation between personality attributes and the social acceptance of retarded children by others. In the general population, one of our strongest predictors of adult adjustment is level of peer acceptance during childhood. We have some evidence about the degree to which retarded children are accepted by their peers under various classroom arrangements, but we do not know much about what characteristics of individual retarded children make for high or low levels of peer acceptance. Such knowledge could lead to important advances in the ability of the mentally retarded to attain satisfying and adaptively useful social relationships.

Finally, as mentioned elsewhere in this document, the transition from school (or institutional settings) into the community is a key life transition for retarded people. We know that some fare far better than others. Research (some using anthropological techniques) suggests that social skills are important and that cognitive skills and work habits may also play a role. But little is known definitively about what determines the success of this transition or about how the social institutions, whose job it is to prepare the student for entry into society and the world of work, can affect that transition.

Conclusions and Recommendations

Study of psychological processes has generated substantial knowledge about the components of intelligence, the tasks of basic cognitive ability, and how mentally retarded people perform on these tasks. What is now needed is research that clarifies the relationships among the whole set of component mental processes, how they interact, and how deficiencies in the information processing system relate to mental retardation. We also need to increase our knowledge of the processes that are fundamental to the development of intelligence from infancy through adulthood, in particular whether relative

abilities are stable over time, or whether they change at different stages of human development.

There are two methodological considerations that should guide future research into these and related issues. First, although much research into psychological processes involves study within a laboratory setting, there is a growing body of relevant research using structured observations of retarded people's behavior in naturally occurring settings. So far, however, investigators with expertise in laboratory methods have tended to address somewhat different research questions and focus on somewhat different cognitive, intellectual, personality and motivational processes from those skilled in observational techniques. As a result, methods tend to be heavily confounded with topics. Ideally the methods should be complementary, with the same constellations of processes examined in both settings. Patterns emerging in only one of the settings should provoke questions with considerable heuristic value. The second methodological consideration is the need for longitudinal studies. Without these types of data questions about development cannot be answered.

With respect to specific areas of research, projects with the following foci should have priority:

- o Distinct developmental processes and knowledge systems, rather than general attributes.
- o Specific (as opposed to omnibus) interventions designed to increase behavioral competence, including not only cognition, but adaptive behavior, temperament, motivation, social skills, and motor development.
- o Base knowledge, strategy use, and metacognition across the full array of developmental levels simultaneously.
- o Collaborative biomedical and behavioral research, especially in medically oriented interventions in which specific behavioral outcomes are at issue. Behavioral measures must be related to specific biological and environmental sources.
- o Connection between motor and cognitive development for children at risk for mental retardation.
- o Generalization and transfer of cognitive, social, and motor skills.
- o Response demand characteristics of specific environments, taking into account social and cultural variables. Multiple measures must be taken in multiple contexts, tapping motivational and personality processes as well as cognitive processes.
- o Comprehensive process-oriented diagnostic methods.

Staff Review

Within the behavioral and social sciences research effort supported by the Branch, research on psychological processes has historically led other areas of behavioral and social science research in terms of numbers of grants and

dollar support. Because psychological processes is a well-established field of research endeavor and with a complement of well-trained investigators, the Branch proposes to continue programming support for these endeavors while reserving specific initiatives to other areas of research judged to be most in need of stimulation and growth.

It should be noted that a conference on motor skills (also emphasized as a priority in section VIII) was held in September 1984 to delineate research needs and opportunities in the area and to chart future research directions. A publication to disseminate the proceedings of the conference is in press.

Action Steps

- o Give programming emphasis to research on development of motor skills.
- o Continue regular research programming in accordance with the recommendations.

IX. BEHAVIOR ANALYSIS

Behavior analysis focuses primarily on the interaction between behavior and environment: the behavior of organisms on the one hand, and the environmental conditions (i.e., the reactions stimulated by that behavior) on the other. Behavior analysis is based upon the scientifically documented observation that future behavior is a function of the consequences of past behavior. Antecedent events discriminative of behavioral consequences have also been studied and constitute an increasingly important methodology for understanding behavior change. Research in this field has emphasized the discovery of ways in which environmental events can be arranged in a contingent manner so as to increase, suppress, maintain, elaborate, or otherwise alter behavior occurring in the future.

Contrast to Other Areas of Psychology

Behavior analysis can be contrasted with other areas of psychology. For example, it emphasizes directly observable and measurable behavior rather than inferred constructs (such as "intelligence") that are the prime subject matter for other areas of psychology.

Behavior analysis provides a number of unique approaches to the study of human behavior. For example, a primary distinction in behavior analysis is behavior excess versus deficit. Basic research on operant conditioning has used the rate of the behavior as a fundamental of analysis. Therefore, behavior is considered to be either increased in rate or decreased in rate. Behavioral excesses (e.g., excessive crying, disruptive behavior, hyperactivity) are considered as problem of rate (i.e., the rate of the behavior should be decreased). Similarly, behavior deficits (wherein a desirable behavior occurs at a very low rate) are problems to be solved by procedures that increase rate. Behavior deficits can also include the lack of an appropriate behavior. In such a case, the solution is one of building on existing behaviors that are prerequisite components. When these components are combined and extended, they then constitute the desired appropriate behavior.

Another important distinction in behavior analysis is the difference between function versus topography of a behavior. In contrast to other more analytical approaches in psychology, the topography of behavior often holds little importance with regard to its ontogeny or modification. Rather, the history of relationships between behavior and contingent events functionally determines how behaviors develop, are maintained and are modified.

A distinction is also made between acquisition of behavior versus its continued occurrence (i.e., maintenance). This distinction is important because the conditions under which a behavior develops may be different from the conditions under which the same behavior is maintained. For example, a behavior may originally be emitted (e.g., a retarded resident in an institution seeking staff attention) in response to a particular set of events which do not occur frequently (e.g., because the resident has accidentally injured himself). However, depending upon the consequences provided by the environment contingent upon this behavior (e.g., the attention of the staff, removal from the unit, medical and other special care), the behavior may again occur but now not in response to the infrequent stimulus events under which it originally occurred, but rather because of the history of consequences experienced (e.g.,

the resident may now begin to seek the attention of the aides and even engage in self-injury in order to guarantee their attention).

Relevance of Behavior Analysis Research to Mental Retardation

Behavior analysis research has shown that performance and skill competence are both a function of and may be improved by the differential responses given to the behavior of developmentally disabled individuals. This research has provided important implications about the ontogeny of developmental disability as it relates to the environment and about the intervention strategies that may be employed to otherwise alter these disabilities. This line of reasoning permits an alternative conceptualization of retardation from the traditional view.

The traditional view is that retarded behavior is caused by either hypothetical psychological concepts (e.g., defective intelligence) or hypothetical biological concepts (e.g., constitutional deficits), which in turn are controlled basically by heredity and modifiable by social and physical interactions. This traditional view of retardation can be contrasted with a behavioral analysis view, which would assert that retarded behavior is a function of observable social, physical, and biological conditions, all with the status of independent variables. In this sense, the behavioral status of retarded individuals is in part the direct result of how the social environment responds to their behavior. This approach has led to significant advances in treatment. Treatment research in behavior analysis emphasizes only those events that can be manipulated and can serve as antecedents or consequences for behavior, because such manipulations are often the only means for modifying performance deficits of the developmentally disabled.

Behavior analysis relates to the general domain of normative behavioral development by demonstrating, through the study of retardation and developmental disabilities, that the change in children's behavior over time (development) cannot be considered solely an automatic process synonymous with neurological elaboration. Rather, the development is the product of an individual's learning history occurring in conjunction with, and in some cases affected by, biological development.

Current Knowledge

The most important conclusion based on research employing learning principles with developmentally disabled populations is that very significant improvements in learning and performance may be achieved with even the most profoundly retarded individuals. Three decades of scientific research demonstrating that retarded individuals are capable of learning, and the extensions of this finding across a wide range of populations and behaviors, have had a major impact on the provision of service to the retarded on a national level. Legal mandates, funding, and programs concerning the mentally handicapped have undergone a dramatic shift in the past three decades. While the rights of these individuals for proper care have never been in question and could have been favorably decided without knowledge of their learning potential, the numerous demonstrations that these individuals can achieve improved vocational, educational, self-help, social and communication skills, and often integration into society have been critical factors in obtaining improvements in educational programs for the retarded. Further, this programmatic change has ultimately resulted in changes in public attitudes.

Treatment. Important advances in treatment can be considered in broad areas: increasing adaptive behavior and decreasing inappropriate behavior. Over the past decade, significant findings in both areas have built upon and extended much of the initial operant research that occurred during the 1960s. The following general areas represent some of the research efforts on the development, elaboration, and maintenance of desirable adaptive behavior:

- o Language - Many studies have extended the operant analysis of verbal behavior to the development of functional language of MRDD populations, including production of generative sentence usage, acquisition of sentence structure, generalized receptive prepositions, and use of sign language as an alternative or adjunct to spoken language.
- o Self-help skills - Recent work has expanded the technology available to teach basic self-help skills. Particularly noteworthy have been toileting programs. Other areas of application with self-help behaviors have been teethbrushing skills and self-feeding, to name a few.
- o Vocational training - Research has been conducted with respect to various aspects of vocational placement, including behavioral assessment of entry-level skills and prevocational competencies, production management procedures, and methods of increasing time spent on task.
- o Community survival skills - This area of investigation, which originated in the 1970s mainly as a result of the deinstitutionalization movement, has been concerned with teaching repertoires that promote independent functioning in community environments. The areas studied have included pedestrian behaviors, bus-riding skills, housekeeping, restaurant skills, clothes selection, leisure-time activities, cooking, and social skills.
- o Behavior modification - This area concerns advances in techniques to reduce the occurrence of certain behaviors. The most significant impact has been in two general areas: (a) the development of effective, publicly acceptable, low-risk techniques to decrease inappropriate behaviors; and (b) the successful treatment of severe and often dangerous behaviors.

Methodology. Methodological contributions have been made in observational procedures and experimental design. Regarding observation procedures, an extensive technology has been developed for measuring various dimensions of human behavior. Systematic analysis has been applied to the accuracy of different observation procedures and methods for assessing their reliability: that is, the degree of agreement between two individuals observing simultaneously yet independently.

Experimental designs have favored time series strategies with individual subjects or small groups of subjects serving as their own control. Single-subject research designs maximize the identification of therapeutic interventions directly applicable to individuals as opposed to altering some aspects of a group mean. This is to be contrasted with group research designs where

statistically significant differences are obtained even though the variables in question affect the behavior of only some of the individuals or, alternatively, affect to a very small extent the behavior of most of the individuals under study.

As with observation methods, researchers have expanded the range and refined the analytic power of experimental techniques, such that new methods of analysis have been generated over the past 10 years, including the multi-element design, changing criterion design, and the multiple probe technique.

Gaps in Knowledge and Next Steps

Despite the progress to date, critical gaps in knowledge currently exist in three areas:

Role of Operant Processes in Ontogeny and Etiology. Basic animal and human operant research has investigated extensively how behaviors are acquired and maintained. However, while research over the past 20 years has unequivocally demonstrated the utility of employing operant principles to solve problems of social significance, this has been achieved primarily by applying these principles in the absence of knowledge about the development of the problems. A logical extension of the research progress to date would be the study of specific behavioral repertoires (considered normal or pathological) in terms of the operant processes involved in their initial acquisition, and subsequent elaboration and maintenance. At a minimum, such research requires a descriptive analysis of the conditions that exist in the social environment, a hypothesis as to how such conditions could influence the behavior under study, and controlled experiments to show that if such conditions were altered according to the hypothesis, then the behavior would change.

In particular, parenting must be studied with regard to the appropriate or inappropriate use of operant principles. The field is generally lacking information and descriptive data on parenting. Much of behavior analysis research implies that parenting practices can result in inappropriate behavioral repertoires; and with MRDD children, parenting may be qualitatively different and unadaptive compared to that for normal children. Unfortunately, in the absence of data on parenting practices, this implication cannot be substantiated.

Extent of Behavior Change. Another gap concerns the ultimate extent to which behavior analysis can effect pervasive, meaningful behavioral changes. Research to date has almost exclusively been concerned with modification of a circumscribed range of behaviors over a relatively short period of time (a year or less). Rarely has research considered the extent of behavior change that could be achieved if operant approaches were used comprehensively and intensively over a sustained period in a child's development. In addition, there has been a paucity of research on the behavioral and physiological antecedents that predispose the occurrence of maladaptive behavior. Finally, and perhaps most important, generalization and maintenance of behavior needs study. Although some research has been conducted on generalization, the variables responsible for the occurrence or inhibition of generalization are not well understood. This is particularly true with regard to applied social problems. Arranging conditions in the animal laboratory to study and control for generalization is much easier to accomplish than studying the same process in a more naturalistic environment. Maintenance (i.e., durable behavior

change) has also been a relatively neglected area of research, at least in part because it requires extensive longitudinal data collection, and involves similar difficulties of observation within a naturalistic context.

Integration with Other Areas of Science. The need for interdisciplinary research is worth stressing here, as well as in other sections of the plan. In particular, the operant principles of behavior analysis have provided knowledge about basic biobehavioral interactions. Contingent environmental consequences can have traumatic effects on the biology of an individual. Knowledge from behavior analysis should also be used in developmental psychology research, addressing the extent to which some stages of development are more critical than others with respect to the effectiveness of behavior analysis interventions. Finally, advances in electronic and computer sciences should be exploited to maximize the influence of environmental factors (programmable devices, equipment, and prosthesis) on the behavior of the severely and profoundly handicapped.

Conclusions and Recommendations

Behavior analysis with MRDD populations has resulted in the systematic replication of research findings across a variety of behavior problems, settings, and types of handicapping conditions. The primary outcome has been the well-documented generality of learning principles and a growing technology for assisting handicapped individuals achieve an increase in skills and adaptive functioning in society. This advancement in knowledge and benefit to the retarded has proceeded from the scientific demonstration of (1) the operant principles involved in learning, and (2) the fact that these principles can apply to the retarded, regardless of diagnosis and classification. This work has implied that other extensions of operant principles would result in equally great advances in knowledge and treatment technology. Specifically, the general body of research to date strongly suggests that: (1) operant processes are critical to normal development and to the etiology of pathological behavioral repertoires; (2) given sufficient time and resources, comprehensive and intensive behavioral programs could remediate the problems of retarded persons to a much greater extent than has been realized; (3) closer interface of behavior analysis with other related areas of science would result in important research and significant new knowledge.

Perhaps the highest priority for future work is development of measures of basic determinants of behavior. Essential to all science is the availability of objective, reliable measures and investigative methodologies that can be employed across a variety of independent variables. The use of match-to-sample techniques in the study of stimulus discrimination research and the various operant paradigms in behavioral pharmacology are two notable examples. Basic research has identified the principles and processes responsible for learning, and subsequent applied research has evolved a technology for the assessment of an individual's behavior occurring in daily living situations. In order to extend basic behavioral research to study normal developmental processes, etiologies of behavior problems of MRDD populations, drug effects on behavior and a variety of other emerging topic areas, measures of the basic determinants of behavior that have generality across chronological ages, levels of retardation, and predisposing neurological limitations will need to be developed. This need is noted elsewhere as well.

Study of antecedent events, generalization, and maintenance is also important. Many behavioral procedures that are demonstrated to successfully remediate problems of the retarded in specific training situations do not evidence the same degree of efficacy for extended periods of time in daily living environments. While the technology now developed for initial behavior change in special training situations is valid across situations, additional processes necessary for successful transfer of technology must be studied. The most critical processes of immediate concern are those involved in setting events and the generalization and maintenance of behavior.

A third area worthy of continued study is the controversial issue of drug therapy as a means of behavior modification. Drug therapy is a prevalent means of behavior modification of the retarded despite the lack of experimental evidence to support the use of many drug therapies and the often dramatic, undesired effects of some drugs. Study of the effects of drugs on behavior and of learning-based therapies as an alternative to drug treatment must be continued.

In addition to research demonstrating therapeutic behavior change techniques, increased emphasis should be placed on the study of operant processes in normal development and on the etiology of specific behavioral disorders. Such research would include that which studied or translated current nonbehavioral (sociological, ecological or personalistic) problems into aspects of behavior amenable to behavior analysis. In these cases, etiology would equate to behavior analysis in terms of behavior changes that--when they happen--constitute normal development, and--when they do not happen--constitute or allow maladaptive or anomalous development.

A supposition of research on specific problem behaviors has been that, given enough time and resources, behavioral procedures employed in combination could dramatically change even the most handicapped individuals. This has, in a sense, always been the "promise" of behavioral approaches. The funding of two to three long-term, intensive, and comprehensive behavioral programs on a few of the most promising areas for dramatic behavior change would permit a great deal to be learned about the extent of behavior change possible and how a comprehensive, long-term program could best be structured.

Finally, behavior analysis is now sufficiently advanced to begin to integrate with other scientific areas of importance to the retarded. Particularly important to target would be: (a) the use of findings from developmental psychology to determine whether optimal periods and behaviors should be targeted for behavioral training, (b) behavioral medicine approaches to the problems of the developmentally disabled, and (c) the use of electronic and computer technology to facilitate the study and use of learning processes with MRDD populations.

Staff Review

Behavior analysis represents one of the most powerful tools in the MRDD research armamentarium for improving the quality of life of persons with MRDD. Its power is recognized in its applied consequences and in the elicitation of ethical and public concerns for effective modification of human behaviors. Staff observations suggest that limited NICHD support for behavior analysis rests, in part, on the composition of peer review groups called upon to review applications. Primary review groups balanced in terms of

theoretical and applied research concerns are essential for research progress to occur in the behavioral and social sciences.

The creation of the NICHD and assignment to it of primary responsibility within the NIH for research in mental retardation created need to effect resolution of overlapping responsibilities with the National Institute of Mental Health (NIMH). Consultations between the two agencies in 1965 resulted in agreement that the NIMH would retain responsibility for research in mental retardation concerned with its psychiatric and emotional aspects. This understanding has remained in force to the present, however, the NIMH is currently re-examining its responsibilities for mental retardation research in consultation with the NICHD.

Action Steps

- o Continue efforts to effect balanced representation of behavior analysis scientists and scientists from the social sciences on primary review bodies.
- o Continue meeting with the NIMH staff to delineate mental retardation research responsibilities.
- o Issue program announcements encouraging research on drugs and behavior and for applied behavioral research, contingent upon agreements reached with NIMH.

X. COMMUNICATIVE PROCESSES

Until 25 years ago, the language development of the mentally retarded and developmentally disabled was virtually ignored. This was partly due to research concentration on speech rather than language development--and the consequent lack of frame of reference against which children with developmental disabilities could be compared--and partly to an adverse view of retarded behavior by speech clinicians which led to the general exclusion of mentally retarded and developmentally disabled children from speech assessment and training.

Research Achievements to Date

In the period since the late 1950s this situation has changed dramatically. Several seminal theoretical works, unrelated to one another, on language structure and acquisition and verbal behavior stimulated considerable empirical research. This led to a recognition of how close the relationship was between language structure and the development of communicative competence and between the acquisition of semantic functions and the emergence of cognitive stages of development. These insights, in turn, facilitated development of comprehensive language programs for the severely handicapped and programs for training children during the early phases of language development.

The procedure underlying the development of such intervention programs may be described as a rational effort to design the best program of instruction that the specialist could fashion and then to refine and improve it through instructional experience and careful analysis of ongoing assessments. The increasing attention to intervention strategies, decision making, and instructional planning suggests that intervention research is becoming more apt in the complex issues of language training. This sophistication is apparent in planning language stimulation programs for infants and preschool children; nonspeech communication board programs for cerebral palsied children; sign programs for autistic children; abstract, graphic symbol programs for severely retarded and multiply handicapped children; and communication programs for severely impaired children.

An important fact about these programs is that they could not have been developed 15 years ago. This highlights the impact of recently developed design technology and psycholinguistic knowledge. Current language research seems to be moving us rapidly toward the development of even more effective language and communication programs.

Perhaps the most significant single accomplishment of the language emphasis with retarded children has been a change in our assumptions of feasibility. Whereas 25 years ago we had limited confidence about teaching language to persons with mental retardation, we now realize that language training may be the most effective system for making significant alterations in the course of their development. Further, we assume that whatever one does for a retarded person's language actually reduces the degree of his/her retardation. These gains have derived from the range of work extending from theoretical to practical application research, and they are leading to a new emphasis on the study of language use as the interface between linguistic, cognitive, and social developments. This new emphasis has the promise of finally bridging the gap between psycholinguistic theory and general developmental research.

Gaps in Knowledge and Next Steps

With all this progress, the task of developing effective means for teaching language to the handicapped has not been completed. A fundamental reason is that the various theories of language have not yet been satisfactorily synthesized. Therefore, the intervention models and programs are not firmly based on consistent and complete theoretical frameworks.

Our contemporary understanding of children with mental and linguistic limitations has been strongly influenced by the parameters and assumptions of two dominant theorists--Piaget and Chomsky. These theorists--both presenting the cognition/language issue from the perspective of normal children--although they have drawn different conclusions, share three central assumptions:

1. The child is a self-driven information-seeker and hypothesis-tester.
2. Children's minds are organized according to global abstract principles that change in systematic ways to become adult structures.
3. Language is a context-free system of propositional meanings and formal structures.

The modern explosion of empirical investigations of handicapped children has cast doubt on all three of these assumptions.

The first assumption is challenged on the argument that children learn language not as a private symbol system, but as a means of communicating with others. Initial language learning and subsequent use is embedded in a social context. The recent perspective allows us to include social factors in our models of language acquisition. The second assumption is challenged by the argument that there are localized areas of rule application, of skill-specific linkage across and within cognitive domains. This emphasis on specific linkages transfers well to the clinical realities of assessment and identification of particular competencies for remediation. The third assumption is challenged by a model of language that emphasizes the contextual influences on linguistic functioning, an emphasis that brings with it a rejection of the competence/performance distinction. Contextual influences can be intralinguistic, interpersonal, and situational. This shift allows us to include all aspects in a model of children's functioning--a return to the clinical reality of a child in a contingent communicative situation.

In short, the theoretical literature regarding cognition and language is in a state of expansionary flux. The current state of the knowledge base leaves us with many unsupported inferences, but gives us the basis for new approaches to the problems of language and cognitive deficits and to procedures for remediating the difficulties.

A crucial point to note is that effective language learning by retarded children is not fully achieved until they can generalize it to the settings, the contexts, and the persons in their lives. Consequently, the final goal for language training is now recognized to be not the learning of new productive or receptive skills in a limited training context, but rather their spontaneous usage within the whole of the child's environment. With the change of programmatic goals has come new requirements including the creation

of generalization teaching skills, assessment procedures for contextual language, more elaborate coding procedures for language data, and a more complete model of language usage. The last of these requirements is essential for determining those conditions which enhance, rather than constrain or extinguish, language usage.

Research on language and communication with respect to the mentally retarded is rendered all the more complex because mental retardation refers to a wide range of children and adults with language and communication skills that extend from near normal performance levels to near zero verbal skills. For this reason both scientists and clinicians find systematic programs of research in language difficult to discuss and to analyze. Other efforts to define retarded functions, i.e., social competence or adaptive behavior, have not suggested a general plan for assessing language and communication performance of the retarded. Recent improvements in defining and operationalizing language and communication behaviors suggest that we now have the means for mounting a unified plan for scaling language and communication performance levels (communicative competence) and thus for placing children diagnosed as retarded on graded levels of language and communicative functioning. One of the requisites for this endeavor is a large longitudinal data base comparing the communicative competence of individuals over time and across defined groups.

Not only does mental retardation cover the whole spectrum of language and communication skill levels, it also covers an extremely diverse set of disabilities and problem states. For instance, some Down syndrome children have predictably severe language problems, but respond well to early programs of language intervention. Some autistic children have especially severe communication disorders and highly variable social responsiveness. Multiply handicapped children may or may not learn to speak, to acquire social repertoires, or extensive vocabularies. And there are disturbed children with thought disorders, attention disorders, or transaction disorders.

More research is urgently needed to map the differential language and communication skills associated with different etiologies. This will enable us to design effective strategies to extend the effectiveness of these skills for different types of children. It will also permit us to use the increasingly sophisticated psycholinguistic methods to study additional dimensions of the developmental problems of such children.

Another major gap in our knowledge pertains to our inability to predict which infants are at high risk for speech/language and communication development problems. The numbers of children who have disabilities that relate to problematic educational outcomes or disruptions in social interaction patterns do not diminish with advances in medical care. Speech/language and communicative development continue as a high priority for this group, yet we lack appropriate assessment instruments for determining the complex and mutual interactional influences of child and environment.

Indices of language development that are predictive of later language and educational outcome are a major need. We lack these types of measures for several reasons, including: 1) lack of longitudinal data preceding and going into the school years on large numbers of children of questionable developmental status; 2) insufficient understanding of how the expressions of a

language disorder change over time; and 3) lack of understanding of the relationship between specific linguistic competence in the early childhood years and those in the school years.

A related major problem is our lack of understanding of the role of the environment in ameliorating or exacerbating the effects of earlier insults or trauma. Several studies of intervention programs suggest that "stimulating" or "responsive" environments can compensate for developmental delay while "inadequate" environments may increase deviance. We should determine the aspects of language that are open to environmental influences so intervention efforts can be targeted accordingly.

Bilingualism should be mentioned here as a factor in mental retardation seen as an increasing problem in the nation's schools. What research has been done shows a division between bilingual children with superior cognitive development and those with an average or less than average rate of development. While bilingualism tends to enhance the "cognitive" abilities of children in the superior range, bilingualism for the average or less than average tends to delay language by as much as a year or more, a delay which is exaggerated in the presence of a linguistic disorder and frequently contributes to the classification of mental retardation. The principles of contrastive analysis (initially developed for teaching English as a second language) are now being used to try to separate the effects of one language or dialect on another from features associated with developmental lag and language disability. Also, we are beginning to understand how different (bilingual) patterns of language can influence the way a language deficit is expressed. A priority item for research is to ascertain whether or not a certain level of intellectual functioning is necessary for the acquisition of two separate language systems. The increasing problem of retardation among bilingual children in our schools makes it imperative to be able to predict at-riskness among these children in time for them to receive special language training.

One of the more promising areas of language for the severely developmentally impaired is known as nonspeech communication--including both supplementary techniques to augment communication and nonvocal systems as alternatives to speech--for persons who cannot manage the oral/auditory and/or the oral/motor systems used in speaking. Although aided (static and graphic) and unaided (dynamic or manual) nonspeech symbol modes are often used effectively, they are not invariably successful. Success or failure can relate to symbol recognition, selection, execution, and production, but perhaps more importantly to use in communicative interaction. We cannot yet a) determine characteristics that suggest implementation of aided versus unaided options, or b) predict the rate of skill acquisition and usage of supplemental systems. Basic election and selection research is needed to understand predictors of success/failure, appropriateness and modes of implementation, and reciprocal issues of individualized assessment and symbol systems features.

In this context, it should be noted that handicapped individuals can benefit directly from the use of instructional models, engineering technology, computer technology (including microprocessors) and simulated environments. Technological advances should now be used by researchers to match the topography of the task with the performance capabilities of the individual and to engineer environments to promote and foster symbolic communication.

Finally, the pathophysiological processes that impair language are not fully understood. There are three main categories. The first is inborn basic structural anomalies, usually hereditary, that reflect as limited talent for language. The second is focal brain lesions resulting from encephaloclastic disease in utero or in early life. These lesions are, for the most part (although not exclusively), nonprogressive causing static aptitude deficits in the face of which learning must progress. The third is the retardations of learning progress that result from deficient or defective early experience (the most common of these disorders are those resulting from primary sensory deficits or depriving environments). To what extent members of this last group have genuine aptitude deficits is a crucial question that remains largely unanswered.

Conclusions and Recommendations

Much progress has been made in the past 25 years in recognizing that effective language use is a combination of linguistic, cognitive, and social skills, and in developing language intervention programs that work effectively for many mentally retarded and developmentally disabled individuals. This progress, however, should not blind us to the fact that a number of urgent issues remain to be resolved. The preceding discussion about what we know and what still needs investigation leads to several general conclusions about research issues and strategies.

The first is that much work still has to be done describing in longitudinal perspective the language and communication problems of the many special subgroups that constitute the mentally retarded and developmentally disabled population. The great diversity of language difference represented in these groups requires the research attention of teams of scientists. Second, the theoretical models for integrating the information derived from descriptive and application research efforts are still incomplete. Until this situation is remedied, we shall continue to have problems in planning and implementing language intervention programs. This necessitates the combining of procedures for describing language and for changing language. The two scientific systems so far have been promoted by largely separate and noninteracting groups of investigators. Their efforts should be merged. Third, research strategies should be designed to interrelate data sets from different settings (home, school, play settings, community sites, etc.) so that we can begin to develop composite pictures of the language performance of retarded children. Finally, the appropriate assessment and evaluation of the wide range of developmentally at-risk children (bilingual, nonspeech, autistic, emotionally disturbed, and cerebrally palsied children with cognitive impairments) requires both the application of computer and engineering technologies and up-to-date linguistic techniques. The formidable nature of such research will require the best efforts of basic and applied scientists.

The design and development of intervention programs of greater inherent power and salience must await development of fuller and more complete theoretical frameworks, and their validation through longitudinal data collection and analysis. Until that time, efforts to achieve greater cost-effectiveness in language intervention programs should rely on formative evaluations, which focus on outcome measures detailed enough so that the effects of training components can be determined task by task and from day to day. Traditional evaluations provide little detailed information about "what works" and what can be reduced or eliminated. Formative evaluations should lead to instruc-

tional efficiencies for teachers, clinicians, and administrators who are ultimately responsible for language training programs and to guidelines for the researcher who continues to work to devise more elegant and cost-effective experimental programs of language intervention.

Specific priority areas for research are as follows:

- o Pathophysiology of language impairment, in particular, the genetic basis of hereditary limitations and the focal brain activity associated with normal and pathological language processes.
- o Longitudinal data on the communicative competence of defined groups of retarded individuals.
- o Functional interrelationships among the syntactic, semantic, and pragmatic strands of language development.
- o Bases of language generalization, linking behavioral and cognitive tactics into a common design, and including the dimensions of time, context, and setting.
- o Derivation, by examination of large groups of at-risk infants, of measures of language with predictive validity for educational achievement to determine the relationship between earlier and later language abilities.
- o Role of the environment in influencing language learning for various at-risk populations, including classroom language use.
- o Differential language and communication problems of "special etiologies," and predictors of at-riskness for bilingual children.
- o Selection criteria and procedures, methods of instruction, and effectiveness of nonspeech symbol systems.
- o Designs and adaptations of current and anticipated technology of microprocessing and related systems for use in environments, symbol systems, and training programs for the severely retarded.

Staff Review

Communicative processes research has consistently received strong encouragement and support from the Branch. Language is a culturally embedded function of social development that is usually learned without explicit instruction. However, for many children with mental retardation and developmental disabilities language is seriously delayed or disordered. Such conditions indicate that the usual conditions for language acquisition are absent, inadequate, or dissonant. In such instances there should be explicit efforts to intervene and to produce an arranged set of conditions to facilitate language. Staff judgment on this issue prompts a proposal to conduct a conference on "The Teachability of Language," to address crucial aspects of language intervention for the mentally retarded.

The need for creation of a longitudinal data base for the language development of retarded children will be evaluated within the broad framework of the proposed plan for a conference on data bases (see section XIII).

Branch staff finds particular urgency in the need to study at-risk infants for the purposes of a) deriving early measures of language that have predictive validity for educational achievement and b) to determine the relationships between earlier and later language abilities.

Action Steps

- o Convene a conference on the Teachability of Language in FY 1987.
- o Place the recommendation for a longitudinal data base for the language development of retarded children on the agenda for the proposed National Conference on Data Bases (see section XIII).
- o Continue regular research programming and support with emphasis upon research recommended in this section, particularly with respect to the later language development of at-risk infants.

XI. EARLY DIAGNOSIS AND EARLY INTERVENTION

In examining research and practice in early diagnosis and early intervention one is struck by the major strides that have taken place in the last two decades. The identification of differentiated aspects of early behavior serves as the foundation for specialized diagnosis of deviancy and intervention to remedy early problems in contrast to general developmental assessments of the past. The proliferation of infant stimulation and intervention programs have provided a rich array of procedures that serve as the foundation for targeting specific interventions for specific problems. The priorities for the future lie in building on this foundation.

Past Accomplishments and their Implications for Future Research

The major empirical finding has been that in many domains of infant behavior little relationship exists between assessments using traditional infant tests in the first year of life and later in childhood. The major theoretical achievement has been the explanation for the lack of these relationships. A developmental approach has emerged that views child development as a product of both the capacities and the experiences of the child. However, this theoretical consideration has not yet been fully incorporated into the way diagnosis and intervention are studied and applied. Most clinicians still base diagnosis and prediction on contemporary physical assessments of the infant, when the outcomes of interest are behavioral ones that are strongly influenced by the child rearing environment.

The paradox that future research must confront is that children with the same initial conditions end up quite differently. This conclusion applies to children with abnormal and normal conditions.

- (1) The majority of infants who graduate from neonatal intensive care units have normal developmental outcome.
- (2) A great number of infants with identified neonatal deviancies have normal developmental outcomes.
- (3) Some children with normal perinatal courses have later developmental deviancies.
- (4) The majority of children with mental retardation have no identifiable organic deviancy.

Given our current developmental model the solution to these paradoxes lies in two directions. The simple direction is to continue the search for assessable variables in the infant that are prognostic of later deviant behavior. These variables should be in the form of factors that will distort the infant's interaction with experience and limit developmental possibilities. At the present time early variables that are most predictive of poor developmental outcomes have not been found in the child, but rather in the childrearing environment. The more complex direction is to search for diagnoses based on the developmental system of "child in context." In this approach the characteristics of the infant are combined with the characteristics of the environment in the assessment process. This approach has not been emphasized in past research on early development, but may be the foundation for future progress.

Early Diagnosis

There is an important difference between diagnosis, strictly defined, and screening. Diagnosis is directed at the identification of specific disorders with clear underlying causes that can then be treated with specific interventions. Screening is directed at the identification of a population that is at risk for developmental problems. Such a population is one in which a higher proportion will have later problems than of other populations. Since development is an epigenetic process in which each new level contains new forms of behavior that depend to some degree on preceding levels, but are also to a certain extent independent of it, few diagnostic categories are valid across developmental periods.

It would seem, then, that diagnostic categories could be built upon new information-processing assessments of young infants. In fact, such scales are being used as described below. But, in turn, the later intelligence of the child will be modified by the information provided by the environment and the motivational capacities socialized into the child. To the extent the environment provides a poorer or richer set of educational experiences and a lesser or greater motivation for learning, the child's intellectual outcome will be better or worse, to a large extent independent of initial conditions.

A diagnosis of cerebral palsy, for example, is based on the detection of a nonprogressive brain lesion that produces motor impairment but not necessarily mental retardation. Because, until recently, all infant behavioral scales required motor responses, these children usually scored as mentally retarded. As these children grew, it turned out that no more than half were still scoring in the retarded range. With the recent development of nonmotor assessments of infant information processing—for example, visual attention tests—many of these motor-impaired infants are performing similarly to nonhandicapped age peers. In the past such children were diagnosed as mentally retarded and were institutionalized simultaneously. And, indeed, they ended up mentally retarded. The retardation, however, has been found not to be the result of the medical condition, but the result of the institutionalization. Currently, it is rare to institutionalize such children. As a consequence, the incidence of mental retardation among them has been greatly reduced.

Since diagnostic categories may not be found applicable in the analysis of infant behavior, developmental screening may be a more fruitful approach for identifying children who will exhibit later behavioral disorders. Current screening efforts have been devoted to the design of easily administered developmental tests to young children. Children who show delays on these tests are then referred to intervention programs described below. The plasticity of the developmental process permits the normalization of behavior in many high risk children who enter successful treatment programs. To the extent that experiences are not improved for these children, their at-risk status is translated into a diagnosable deviancy. Future directions in diagnosis should be to combine assessments of the child and the environment, so that the strengths and weaknesses of both can be combined into useful categories for targeted intervention efforts. Different types of assessment have differential promise in this regard.

Biomedical Assessments. Diagnosis during infancy has been exclusively based on medical rather than behavioral criteria. Medical diagnoses of perinatal

anomalies may be the limit of what can be achieved in this area. Sensory and motor handicaps such as blindness, deafness, and cerebral palsy are valid biological diagnoses that will generally remain as continuing factors in child performance. However, these factors are not prognostic of deviant behavioral outcomes. Research has found that with appropriate childrearing and educational interventions, children with such disorders can have normal cognitive and social outcomes.

Neurological abnormalities have not lent themselves to either clear diagnoses or clear prognoses. Chromosomal anomalies such as Down syndrome, certain forms of cerebral palsy, and perinatal complications (such as severe intraventricular hemorrhage or very low birth weight) have been found to have moderate to high correlations with later cognitive and some social deficits. However, these relationships are neither universal nor are they specific for any individual child. In other words, causal links have not been identified between these initial conditions and behavioral outcomes.

The conclusion that can be drawn from this previous research is that biomedical criteria can serve as one source for defining a group at high-risk for behavioral problems, but cannot be used to identify diagnostic categories.

General Behavioral Assessments. In the past research on behavioral diagnosis of infants has not produced useful results. Several neonatal behavioral assessment scales have been developed but their utilization has produced neither stable scores nor predictable outcomes. More traditional scales of infant development have been available for many years, but their generality and diversity of content have produced neither specific behavioral diagnoses nor predictions. The conclusion that can be drawn from this research is that general scales of infant development may be used to identify populations at risk for later behavioral problems but not as diagnostic measures. A number of researchers have argued that social competence and adaptive behavior are more relevant criteria for both development and intervention, because the individual's ability to cope with and live in society will be the ultimate criterion, not his or her intelligence quotient.

Specific Behavioral Assessments. While the general behavioral assessments have not been fruitful in either diagnosis or prediction of developmental disabilities, recent research has pointed to a number of measures that may be more effective evaluation instruments. The major shift in this research is the attempt to study behavioral processes that underly the commonly used performance measures.

Measures that seem to show most promise are those that assess the infant's characteristic response to stimulation in terms of such variables as attention, manipulation, and play. Early measures of infant visual attention, habituation, and preference for novelty have been found to differentiate among groups of infants varying on medical risk factors. Preterm infants, as a group, are slower to process visual information than full-term infants, as a group. Furthermore, within the preterm group, those infants who show the longest attention to unchanging stimuli are also most likely to have lower scores on developmental scales at 5 years of age. Visual recognition memory inferred from the 3- to 7-month-old infant's tendency to devote more visual fixation to a novel than to a previously seen target, appears to be related to developmental scores at 3 years of age. High degrees of accuracy were

obtained in predicting children that would later score in the retarded range. A major question about these processes is whether they are only reflecting still deeper components. Research questions that need to be answered include whether the differences in attentional performance are the result of differences in the capacity to modulate arousal, speed of information processing, or interest in novel stimuli.

Studies of exploratory behavior from 8 to 12 months of age have found relationships with later developmental scales. Touching objects, turning them and transferring them from hand to hand provides information that can be related to concept formation and early language. On the other hand, such exploration may only be a reflection of neuromotor development because in some studies the relationship of exploration to later IQ scores was found only when children with motor impairments were included in the sample.

During the second year of life functional play has been found to be assessable in children with a wide range of impairments and to be related to later language performance more strongly than sensorimotor skills assessed at the same time. A number of other such behaviors may be identified that reflect processes more closely related to deficits in the child and subsequently to later intellectual functioning.

While much of the concern with deviancy has focused on cognitive functions, this may be a misplaced emphasis when the goal is to produce children who are competent to fulfill the social aspects of roles in a culture. The use of cognitive criteria as outcome measures for the effects of high risk conditions or intervention programs may be highly questionable. Longitudinal studies have shown that the intellectual competencies of high-risk children are in the normal range, while social and emotional competencies may be severely compromised. In studies of children with conditions ranging from respiratory distress syndrome to malnutrition, IQ scores at 5 to 8 years of age were independent of infant disorders, but problems of social interaction, motivation, and affective disorders were related to the initial conditions.

Research is just beginning on the social competence of young children, but some of the leads may result in contributions to our understanding of the developmental process. Motivation and temperament are important moderators of social exchanges. While there is agreement about the significance of these variables, there is still controversy over the operationalization and assessment of these factors. Social exchanges between the infant and the caregiving environment are important not only for the development of social emotional competency but also for intellectual development. The analysis of infant-parent interactions has produced a rich data base of normative patterns. Interactions between parents and handicapped or high-risk infants are the target of many early intervention programs to be discussed later.

Environmental Assessments. One of the more exciting directions taken by current research is the analysis of environmental factors that impact on child development. Earlier behavioral researchers had identified demographic variables such as social status as important determiners of developmental outcome. In terms of predicting intellectual status after infancy, family educational and occupational level has explained more of the variance than biomedical or behavioral assessments of the child.

As in the case of infant variables, however, no environmental factor has been identified that has a causal relationship to a particular deviant child outcome. Multivariate models have been used to demonstrate relationships between the number of environmental risk factors and deviancies in both later intellectual and social competency. The more negative factors in an infant's environment, the lower the child's intellectual and social competence. A topic for future investigation in this area is the examination of parents, who, despite massive numbers of risk factors, provide an excellent developmental environment for their children. One of the factors found in such families is a strong commitment to religion.

Early Intervention

In the early 1970s only a few pioneer early intervention programs for the mentally retarded child existed. Now a network of such programs has been established throughout the nation. The emphasis of these programs is shifting from whether it is possible to develop programs for young disabled and at-risk populations to issues of how to improve the quality and effectiveness of various approaches and procedures. While the sophistication of program implementation has grown dramatically over the last 10 years, there has not been an equal growth in the quality of program evaluation. Seldom, however, do critics appear to appreciate either how recent the early intervention enterprise is or how many methodological problems still confront intervention researchers.

Treatment Populations. One of the basic issues in early intervention is the question of identifying the target population. Intervention may be addressed to disturbed infants and their parents (as in failure-to-thrive cases of developmental disabilities), or it can be directed toward broader risk groups (as in teen-age parents or parents of preterm infants). For the former groups there is a clear clinical rationale because the child shows some problem that needs some form of treatment. For the latter groups the children may show no contemporary signs of deviancy and the vast majority will not show deviancy in the future. In these situations the purpose of the intervention becomes ambiguous to both the professional and the parent. Simply put, is the goal of early intervention to promote equality of achievement in children, regardless of the level of achievement typically attained by children in similar social circumstances, or is the goal to minimize the effects of biomedical complications so that the children will be free to seek their own level of adjustment determined primarily by their social circumstance?

As noted, despite the physical pain and handicaps associated with many biomedical abnormalities, the consequences for later social, emotional, and intellectual competencies are more closely tied to environmental circumstance than to biomedical condition. Thus the social policy and diagnostic questions are intimately related.

Intervention with Infants. Although the behavior of young children has not been seen as deterministically related to later achievement, there is general agreement that later achievements are based on earlier ones. Programs for handicapped children have provided educational, motor, sensory, linguistic and social interventions in efforts to reduce the effects of developmental disabilities. Educational programs have been highly successful with children who were formerly believed to be uneducable. Down syndrome children have

shown the greatest gains in this arena, many scoring in the normal range on preschool developmental scales.

Many strides have also been made in motor therapies. A short while ago most of the physical therapy done with infants was by clinicians trained for work with adults. More recently there has been a major increase in the number of therapists trained specifically for work with infants. Motor therapy has produced dramatic improvement in some handicapped children and has been generally beneficial for all handicapped children in facilitating their learning activities by training parents and educators to properly handle and position the child. However, there has not yet been a major evaluation of the efficacy of these programs for improvements in motor skills that would not be attributable to developmental processes alone.

Evaluation of the effects of motor therapies is a good example of the difference in orientation provided by a developmental vs. a diagnostic deviancy approach. In the latter case the goal is to cure the problem, in the former it is to prevent the problem from creating later problems. From the developmental perspective programs that do not cure the motor impairment are not a failure as long as they prevent later social and intellectual problems. If a program is able to position the child so that, despite the motor handicap, the child is able to learn and interact with his or her social environment, then that program has successfully addressed its goals for behavioral development.

Studies during the neonatal period have been carried out to demonstrate the efficacy of a variety of such interventions, including waterbed flotation, extranutritive sucking, extra rocking, and extra stroking. These studies with relatively small samples of children require further investigation to determine the limits of their effectiveness. While interventions with handicapped children primarily take place in community programs, interventions with high-risk infants generally occur in the hospital setting in which the children are identified. Upon graduation from neonatal intensive care units, the children are in the care of their parents. Parents have become the targets for continuing intervention efforts, since there is a general agreement that infant programs require involvement and training of parents as well as the target children.

The different settings for high-risk and handicapped child intervention programs are also reflected in different disciplines taking responsibility for the intervention. In the hospital responsibility falls primarily to nurses and motor therapists, in the community to special educators. The split between services provided by the medical community and those by the educational community has created problems for families when the child is discharged from the hospital. One of the major areas of progress in early intervention is the development of procedures to help the parent make the transition.

A question that needs to be better answered is whether positive outcomes reported for current hospital infant intervention programs are the result of treating the child or the parent. Are later developmental gains the result of activities in the hospital or are they mediated through the parents' subsequent efforts to foster better developmental outcomes for their children?

Early Intervention with Parents. The involvement of parents in the educational process has included three main approaches. One approach is to use parents as paraprofessionals to extend the role of therapists by augmenting educational activities in the program and by continuing activities at home. The second approach is to provide parent support groups in the program to deal with problems of adjustment to a handicapped or at-risk child. The third is to promote parent-child interactions.

Using parents as teachers has produced many positive achievements in cost-effectiveness and intensity of intervention. Various programs have found increases in child performance in a variety of domains of assessment including language, cognition, and motor skills. Balancing these achievements have been costs to the parent-child relationship in terms of the parent becoming less of a parent and more of a teacher, as well as major changes in the structure of the family and the roles of family members.

Parent counseling has ranged from individual psychotherapy to social gatherings. Such programs have offered support, education, emotional development, and assertiveness training. The results of these programs have been interpreted as increasing the competencies and resources of the participating parents. However, few reports of the actual content of these programs or their evaluation have appeared in the literature. Furthermore, there have been few analyses of the effects of parental counseling on the development of the target children.

Parent-child interactions have been demonstrated to affect cognitive, language, and emotional development in children. Because such interactions are frequently disturbed in handicapped children, they are a target for early intervention. Training parents to observe their child's cues and responses has been found to increase positive emotional expression in the interaction. Despite the success of such programs, however, it has not been clearly demonstrated that the child's performance increases in other developmental domains.

Conclusions and Recommendations

Early Diagnosis. The central problem with respect to research in the early diagnosis of behavioral deviancy is lack of knowledge about the developmental relationships between infant assessments and status later in childhood and adulthood. A second problem is that there is not enough information on different domains of behavior within infancy to permit separation of those dimensions that may have greater import for later development from those that may be less relevant or irrelevant. On the one hand, early diagnoses are usually made on the basis of biological criteria without a clear understanding of the process by which biological problems are or are not translated into behavioral ones. On the other hand, behavioral diagnoses may be made without a clear sense of the underlying biological disorders that constrain variation in later development.

The number of infant factors whose interrelationships must be addressed include biological status, nutritional status, motor capacities, temperament, motivation, adaptive behavior, information processing ability, and most importantly, the opportunity to develop provided by a supportive caretaking environment. The factors that go into an assessment of a supportive caretaking environment include family attitudes, knowledge and intelligence,

acceptance of the child, sociocultural norms, parent-child interaction patterns, coping abilities to buffer the child from stressful life events, and formal and informal social support systems.

Research should be emphasized that recognizes that developmental outcomes are the product of the interaction between children with specific strengths and weaknesses and parents with specific attitudes, knowledge, and coping abilities. Areas of particular research priority include:

- o Development of behavioral assessments of infants that tap intellectual processes (e.g., attention, exploration, and organization of play) that may be independent of performance handicaps and environmental experience.
- o Development of diagnostic and screening assessments of the caretaking environment.
- o Investigations of adaptive behavior, temperament, and motivation that constrain or amplify the child's ability to benefit from experience.
- o Identification of those characteristics of infant behavior that are influenced by variations in parent interactions and those that are not.
- o Inclusion of children that vary on demographic, sociocultural, or family organization variables in order to assess interactions with developmental status.
- o Exploration and delineation of cost-effective strategies for assessing and monitoring children who are biologically or environmentally at risk.
- o Development of diagnostic assessments that will provide useful data for early intervention (strengths and weaknesses of child and family).

Early Intervention. Early intervention programs have primarily been developed by clinicians and educators to meet the therapeutic needs of their clients. Historically, it has been parent pressure rather than research findings that has stimulated the creation of most programs for the handicapped. Ethical concerns about depriving children of needed treatment and the lack of research and evaluation training of most clinical personnel have hindered proper validation of most early intervention efforts.

Most programs use a single intervention model with evaluation data provided by before and after assessments. A number of programs have used nontreatment control groups, but there have been few studies using random assignment of subjects and almost no attempts to compare two or more intervention strategies within a single program. This reflects the state of a field where many resources have been available for demonstration programs, but fewer for experimental research. In addition, the field has been beset by methodological problems that have not yet been solved in other, more academic contexts. These include matching of subjects and criteria for change.

The heterogeneity of handicapping conditions combined with the heterogeneity of demographic variables requires large numbers of subjects to test any program. Yet most programs have neither the funding nor staff resources for such efforts. Thus, statistical methodologies are required that can deal with complexity of independent and dependent variables in developmental systems. Most analyses have been based on simple correlational techniques or single comparisons between variables without appeal to better, if still less than ideal, multivariate regression techniques.

Another major problem in the provision of early intervention has been disciplinary fragmentation in the separation between medical and educational communities and target fragmentation in the separation of the treatment of the child from the treatment of the family.

Research should be emphasized on early intervention projects that target specific aspects of the child or environment with specified early intervention procedures using models for research design and analysis that include causal hypotheses about interactions between characteristics of the child, the family, and the social context. Areas of particular research priority include:

- o Comparisons of different intervention strategies in well-controlled designs (e.g., ones that use random assignment of children into treatment groups).
- o Identification of which intervention efforts are effective for all combinations of child handicap and parent characteristics, and which more specialized efforts need to be developed for specific combinations of child handicap and parent characteristics.
- o Study of the effects of motor therapies on the future course of motor development and the facilitation of educational and social interventions.
- o Development of intervention programs to increase parent interaction behavior that promotes child intellectual and social competence within the natural framework of the parent-child interaction, capitalizing on assessed strengths of the parent and child.
- o Study of differences in social and cultural variables that influence the effectiveness of specific intervention strategies.
- o Ascertain whether coordination of pediatric referrals and early intervention programs increases treatment effectiveness.

Staff Review

Early identification and early intervention for infants at risk for MRDD has been an area of primary research emphases for Branch programming from 1966. From the first year of this programming effort, research grant applications concerned with infants at risk due to depriving environments predominated and most were concerned with psychoeducational interventions. Applications for research on early identification and early intervention for biologically vulnerable infants lagged. Beginning in 1971, the Branch initiated contract

programming to stimulate interdisciplinary research in this area for biologically vulnerable infants. Research activity in this area has since grown and prospects for still further expansion are good. The MRDD Branch proposes continued strong programming on early identification and early intervention for infants at risk because of its potential for prevention and for the support and assurance these activities afford families during their children's early years.

Action Steps

- o Issue RFP to develop methods for assessment of caretaking environments.
- o Issue RFA on families with handicapped children.
- o Issue RFA for research on effective intervention strategies which facilitate parent interaction promoting competence with emphasis on effective social and cultural variables.
- o Hold conference on attention, temperament, motivation, exploration and play in mentally retarded children.
- o Issue RFA to study coordination of pediatric services and early intervention programs.
- o Issue RFP to study the effects of motor therapies on motor development and on the facilitation of educational and social interventions.
- o Continue programming of research on developmental follow-up of biologically and environmentally at-risk infants.
- o Monitor contract for development of assessment strategies for identification of biologically at-risk infants.
- o Continue regular programming with emphasis on the other recommendations.

XII. SOCIOECOLOGICAL PROCESSES

Research on social and ecological perspectives bearing on mentally retarded persons was slow to begin and has only achieved limited sophistication in the past decade. Prior to this time, research on the social adjustment or adaptation of mentally retarded persons focused primarily on simple trait measures of the person (such as IQ adaptive behavior or personality scales) rather than the interaction between modifiable attributes of the person and his or her changing environment. The shift from almost exclusive emphasis on traits of the person to one that emphasizes person/environment interactions has been slow in coming about and is even now in a state of transition.

The methodology for examining this interaction has been in place for many years, involving as it does naturalistic observation, ethnographic research, and life history reporting, as well as systematic observation of specific activities in multiple settings. However, this research technology has had only limited application in the field of mental retardation. In past years, research has centered on test procedures, interviews in offices, and limited observations in institutions and other settings. Specific research, even follow-up studies of individuals released from institutions to various community settings, has relied primarily upon data collected by interview, typically with persons other than the retarded individual himself or herself. Thus, family members, employers, social workers, care providers, and case managers have been asked to provide second-order data about the lives of mentally retarded persons. Those lives and the mentally retarded persons themselves have remained relatively neglected.

State of Current Knowledge

Despite the slow and partial application of the full range of behavioral science research methodology in the field of mental retardation, some significant advances in knowledge have been made.

First among these is the realization that mentally retarded persons can, and should, be studied in the full range of their naturally occurring activities and that they should be encouraged to speak for themselves as would members of any other population of interest. The days when mentally retarded persons were considered unreliable witnesses concerning their own lives, their own histories, and their own aspirations are behind us.

It is also now apparent that simple measures of individual attributes, such as IQ, are not predictive of community adaptation. Without other measures of the person and without a much broader range of understanding about environmental demands, understanding of community adaptation cannot progress. It has also been rather clearly shown that social competence is not fixed early in life, nor can it be assumed that competence is organized by a general factor, like intelligence. Instead, social competence appears, to some degree at least, to be setting-specific. And there is general agreement that social competence tends to improve as a function of the length of time spent in community adaptation. Whether this improvement is a function of delayed psychosocial maturation or is simply a result of gradually learning to cope with environmental demands is not yet known.

Further, it is now clear that cultural differences play a part in any understanding of the lives of mentally retarded persons, including the

etiology of their social incompetence and the outcome of any effort to ameliorate their life circumstances. Thus, it cannot be assumed that criteria established for the understanding and measurement of social competence or community adaptation based upon white middle class standards can be meaningfully applied to subcultures as disparate as those found in Appalachia, inner city ghetto populations or newly arrived Asian or Hispanic migrants. This point is confounded by social class, or socioeconomic status, since it is also clear that a great many middle class white mentally retarded persons undergo what could be called 'downward drift' from middle class cultural standards to those of lower SES persons. This downward drift is particularly visible in urban areas and is increasingly like that seen among the institutionalized mentally ill persons or so-called "street people."

The interaction between class and culture is particularly significant because one of the most prominent findings in this field is that expectations--whether those of care providers in a residential setting, family members in the process of socialization, or of peers in independent-living arrangements--exert powerful effects on at least some behaviors related significantly to the outcome of community adaptation. This is not to say that labeling in some simply construed linear-causal model determines the life chances of mentally retarded persons. But it is to say that consistent expectations, whether those of service delivery personnel in, for example, a sheltered workshop or those of other mentally retarded persons living in an apartment building, have a very important effect on the kinds of behaviors and the degree of social competence which those persons develop. Identified as "culture," these shared and patterned expectations refocus our attention away from the inadequacies of the individual and toward the interactive environments in which persons adapt with one another in response to changing circumstances, changing personnel, and changing requirements of everyday life.

Major Gaps in Knowledge

The advances made over the last decade still leave many important and conspicuous gaps in our knowledge.

The first gap, which has been noted elsewhere in this report but is worth reemphasizing here, is that epidemiological data are scanty. Far too little is known about the numbers of persons who are, or could be, considered mentally retarded by psychometric criteria or by community consensus. Without more extensive efforts to enumerate cases, we shall not only remain unsure about the numbers of persons who may require services, we shall also remain uncertain regarding the presumed differential in the percentage of mentally retarded persons among various low income, ethnically different populations.

In addition, the etiology of mild mental retardation remains unresolved. That it is clearly linked to a complex of factors which are disproportionately present among poverty populations is no longer disputable. However, the effects of those many factors (teenage pregnancy, malnutrition, maternal infection, alcohol and drug use, trauma, and the entire complex of factors connected with early socialization) cannot yet be separated. The need for large-scale, multidisciplinary research combining epidemiological models with state of the knowledge behavioral science research concerning etiological variables must take the highest priority--both in terms of establishing a reliable data base and in terms of identifying those phenomena which have the

greatest etiological significance and, therefore, might most readily be targeted for preventive intervention.

In addition to these most fundamental epidemiologic and etiologic issues, there is a continuing and compelling need for more research on the processes by which mentally retarded persons learn to cope with the everyday demands for competence in their lives. Heretofore too much emphasis has been placed on the study of residential environments and too little on other environmental demands--whether these demands involve transportation, leisure, interpersonal skills, or economic productivity. More needs to be known about the specific demands of specific environments and tasks, as well as the tactics and strategies which mentally retarded persons might effectively employ to meet these demands.

In this regard, it is apparent that institutionalization in the United States is predicated on movement toward productivity and independence as crucial indicators of greater normalcy; it is also apparent that too little is known about the pathways along which mentally retarded persons achieve greater independence and productivity. Studies of social support systems, for example, are still too few and too rudimentary. Far too little is known about alternative life styles along a continuum toward independent living, especially alternatives that call for cooperative arrangements to facilitate recreational activities, residential success, and economic productivity.

In a related matter, the effects of socialization for competence (in contradistinction to incompetence) have not been sufficiently explored. Too much research effort has been spent debating the putative effects of labeling in early life or in educational settings, and too little research has been focused on the continuing mechanisms by which children and adults are systematically socialized to be more or less competent and independent. This research would necessarily involve early socialization in family settings, but it would also necessarily examine cultures into which such people move later in life--such as sheltered workshops, independent-living training programs, cooperative apartments, and the like. The phenomenon of learned helplessness is a particularly insidious one which begins early in the lives of many mentally retarded persons and is continuously reinforced.

Quality of life and life satisfaction among various kinds of mentally retarded persons should receive more careful analysis. Too often it is assumed that standards of life quality established by care providers, service planners, and other well-intentioned, but conspicuously middle class, persons should be sufficient for the life satisfaction of mentally retarded persons of all backgrounds, ages, and ethnic origins. That these mentally retarded persons might prefer qualities of life which differ, perhaps even dramatically so, from those prescribed by most habilitation plans and service systems seems undeniable on the basis of available research. It is also undeniable that little research effort has been devoted to determining the criteria which mentally retarded persons themselves would use to assess their own satisfaction with life. Choice is inherent in the concept of normalization; but the freedom to choose differing qualities of life has seldom been provided to mentally retarded persons, and the consequences of allowing such persons to choose qualities of life (e.g., like those of lower income, inner city people) have not been studied.

Another major gap in existing knowledge concerns changes and developments over the life span. There are consistent research findings that, in general, the success and quality of community adaptation tends to improve over time. There is other research, however, which suggests that this is not a continuous or linear progression--that there are many ups and downs, dramatic changes and fluctuations, and even periods of extraordinary adversity and retrogression. Life span research is sorely lacking. What is normative for mentally retarded populations over their life span is not known. Nowhere is this gap clearer than in the almost complete absence of information about aging or elderly mentally retarded persons.

Finally, far too little is known about persons who are both mentally retarded and mentally ill to some significant degree. Since this population is large and presumably growing and since provision of care to such individuals is often inadequate or sometimes totally lacking because of program eligibility restrictions, it is important that persons suffering from multiple disabilities of this kind be identified and that their community adaptation be highlighted. The socioemotional risks confronted by mentally retarded persons are considerable in and of themselves. When those persons also have some degree of mental illness, those risks may become insupportable and may have untoward consequences for society. In this regard, although a great deal is now published regarding the antisocial or criminal behavior of deinstitutionalized mentally ill persons, too little is known about deviant behavior by deinstitutionalized mentally retarded persons.

There are many other research needs, large and small, that could be specified. However, most important is the need to study the lives of mentally retarded persons in their totality. They have been studied in pieces: Their residences have been studied, their roles as economic producers have been studied, as well as their suitability as parents and their difficulties with certain tasks. But all too often, their lives as a whole have been ignored. Until these lives have been examined systematically over time, it makes limited sense to identify and separate out arbitrary aspects of their experience as focal concerns.

Indicated Strategies for Future Research

It is apparent from our comments about gaps in research, that research strategies to be fruitful must employ holistic perspectives on the entirety of the lives of mentally retarded persons over their life spans. Life span research must ideally be longitudinal, although it may also include some cross-sectional design features. Holistic research may follow any of a number of ecological models, but it must have added space for the understanding that what is important in the lives of human beings cannot be determined simply by outside criteria. It is essential that the human beings at issue participate in the process of defining what is significant to them.

It should also be apparent from what has been said before, that research on the phenomenon of mental retardation must remain limited in its effectiveness to the extent that persons defined as being mentally retarded are only those identified by, and known to, what can be considered the mental retardation service delivery system. Since these persons, identified early in life or during school years, constitute a minority, albeit a substantial one, of all presumed to be mentally retarded persons, their needs and life experiences may also be presumed to differ from persons who are not identified and are not

receiving services. It is important that persons who were once served by the mental retardation service delivery system and subsequently lost eligibility in those services be identified and their life courses studied. It is also important that persons who are psychometrically retarded or retarded by community consensus be identified and studied and their life prospects compared to persons who are similarly mentally retarded but receiving services from one or another agency.

In this regard, research in various culturally different populations, including new migrants to the United States, would be particularly desirable. Research in other societies, whether industrialized or not, would also be instructive. The Western European experience with mentally retarded persons is, after all, an experience related to a particular type of culture; it is not a universal one. How the mentally retarded are identified and responded to throughout the Third World could provide useful correctives to our own ideas on these matters.

Whatever the populations of study, it is important that longitudinal research employ multiple disciplines using multiple methods of data collection and analysis and multiple comparison groups. Ideally these should include, as mentioned, mentally retarded persons identified psychometrically, mentally retarded persons not yet identified or known to an identifying agency, and persons who are not psychometrically retarded yet are socially incompetent in one or another domain of life, for example, persons who are illiterate. This last point is particularly crucial. To the extent that mentally retarded persons are studied in vacuo, our understanding of them and our society will remain limited. It is important not only that the entirety of the lives of such persons be examined, but that their handicaps and their successes be studied. And it is important that this be done not only in comparison with persons handicapped in other ways, but in comparison with persons considered not handicapped whose "cultural success" or socioeconomic decline could provide an instructive contrast. If research concerning mentally retarded persons is reconceptualized in this broader way, benefits will accrue not only to the mentally retarded and their families, but will also help identify the needs of other children and adults, and sharpen societal awareness of the dilemmas which we face now and can anticipate in the future.

Conclusions and Recommendations

In addition to the points made in section II on Epidemiology, there is a pressing need to identify (1) persons who are psychometrically (or consensually) mentally retarded but not receiving services as mentally retarded persons, and (2) document the life courses of persons whose eligibility for services was terminated. Because the issues here are methodologically complex and the required research could be inordinately expensive, a conference/symposium is the most appropriate first step in developing cost-effective research strategies.

Research that encompasses the life span of mentally retarded persons is badly needed. At present, the aging or elderly members of this population are virtually unstudied, and knowledge of cultural, regional, and social class differences in the development of social competence and the achievement of life satisfaction are badly neglected. Research should focus on the continuities and discontinuities in life span. Both cross-sectional and longitudinal designs should be considered.

Issues of quality of life and life satisfaction among various kinds of mentally retarded persons should receive greater attention, including determining the criteria which mentally retarded persons themselves would use to assess their own satisfaction with life. The concept of choice is inherent in that of normalization, but the freedom to choose differing qualities of life has seldom been considered for or provided to mentally retarded persons.

Research is needed that identifies the experiences and interactions that lead to improved social competence. This research would necessarily involve early socialization in family settings, but it would also necessarily examine cultures into which such people move later in life, such as sheltered workshops, independent living training programs, cooperative apartments, and the like. This research must be sensitive to both overt and covert aspects of the contexts in which competent performances are learned.

Staff Review

Socioecological research in the area of MRDD has not kept pace with research needs and opportunities. The social action programs of the past 25 years on behalf of MRDD persons have greatly expanded their opportunities for participation in a fuller range of life activities. In this context, social competence has emerged as a critical variable within the range of MRDD research concerns.

The social adaptation of persons with MRDD to the complexities of community life is not accomplished without stress. Reports to staff from internists and MRDD-oriented pediatricians working with older persons with MRDD indicate growing concern with their general health care after school age and frequency of psychosomatic illnesses (ulcers, hypertension) in this population. Because MRDD research and services have been concentrated on the early developmental years, few studies on the health and problems of social adaptation of older persons with MRDD have been reported. This latter area is one of potential overlap with other agencies.

Action Steps

- o Issue a program announcement on quality of life among MRDD persons especially those of minority groups.
- o Hold a conference on the measurement and development of social competence in MRDD individuals.
- o Confer with staffs of the Administration on Developmental Disabilities (ADD) and the National Institute for Handicapped Research (NIHR) regarding their interest in studies of health and health care of persons with MRDD past school age. Issue an RFP on this issue contingent upon outcome of meeting with ADD and NIHR officials.
- o Hold a conference on adaptation to postsecondary education settings such as sheltered workshops, competitive work settings, and group homes.
- o Issue an RFA on transitions to post secondary education settings
- o Continue regular research programming with emphasis on the other recommendations.

XIII. FAMILY AND COMMUNITY

Family and community issues are important to the prevention and treatment of mental retardation and developmental disabilities and to the enhancement of life quality for persons suffering from such disorders.

This section of the plan divides these issues into three major categories, each of which is discussed in turn: research for prevention of mental retardation, research on ameliorative programs for retarded persons and their families, and monitoring the prognosis of mentally retarded persons in the present system of care. These discussions are followed by a brief overview of ethics and mental retardation. The section ends with conclusions and recommendations, staff review, and action steps.

What Is Known and Priority Areas for Further Research

Research with Families and Community for Prevention of Mental Retardation. It remains true today that diagnosticians are unable in many, perhaps a majority of cases, to identify the specific etiology of an individual's mental retardation. Nevertheless, every few years specific sources have been determined for specific syndromes involving mental retardation, and for each the question of direct prevention can then be raised. We have, for example, recently witnessed the identification of the fragile X syndrome and the fetal alcohol syndrome. For the former it is not presently conceivable that prevention via research in family and community can be achieved, except through carrier identification and genetic counseling (see Section IV for further discussion).

For fetal alcohol syndrome, in contrast, even though the causative agent of mental retardation is understood (see Section V for further discussion), prevention cannot occur without public information together with family and community strategy.

Fetal alcohol syndrome is but one of several specific contributors to the rolls of the mentally retarded where the specific agent of damage is comprehended but in which preventive steps must involve sociobehavioral action in a context of broad public support. These include lead ingestion, head injury through physical abuse, disciplinary shaking, failure to employ auto seat restraints, ingestion by pregnant female of substances other than alcohol, and failure to employ appropriate pre- and postnatal care, including vaccination and proper nutrition. Preventive steps through expanded family and community knowledge and action are required to meet these issues.

Epidemiological studies are required for several reasons. First, it is not fully understood how person-drug interaction operates, whether some subgroups or persons are more susceptible to such agents as alcohol than are others. For instance, it is reported that Eskimo women who drink are at a one in four risk of producing a child with fetal alcohol syndrome. Preventive steps, thus, are needed more in some population groups, and public information, procedures of identification of cases, generation of persuasive forces, etc., will have to be fitted to the target population.

Once identified, the subgroup populations must be examined in detail, using participant-observer continuous or repeated contact over an extended period, the critical time being on the issued being studied. Certainly one of the priority issues is the basic beliefs and the values and sources of values

individuals hold. For example, pregnancy may hold no stigma for a single black mid-city girl, and no strategy of encouraging contraception yet appears to be fully effective. Similarly, teenage youth are beholden to peer values far more than to other forces, and family is regarded more sacred than, say, teachers and police. To determine just how to change values and to produce some sense of consciousness and responsibility about having children and protecting the health of such children requires investigations of the transactions made between target youth and peers, family members (including extended family members), and other members of the general social support network. It will be necessary to employ a systems approach to identify such influences and find points at which counterinfluence can be introduced. Analogous effort must be addressed to parents whose beliefs (e.g., rejection of authority) lead to abuse and neglect of children and risk toxic or physical injury. Several leads already exist regarding the dynamics of child abuse, including the reality that the child contributes unintentionally to abuse by being disabled, unwanted, or sickly.

Some leads can come from parent education in various contexts, including programs of teaching parents how to be effective parents of handicapped children; how to cope with behavior problems; how to avoid circumstances leading to abuse. We do not yet know where are the points of penetration and introduction of change in the teenagers who will have handicapped babies, but we know from the parent education movements that some procedures do work with some groups of individuals.

Research on Ameliorative Programs for Retarded Persons and Their Families. In the last decade policy has clearly favored community residential placement over large institutions. One result has been the rapid accumulation of out-of-home placements that are located in the community, but vary widely in size, staffing, degree of disabilities manifested by clients, and a host of other variables. It has also increasingly protected parental rights. Parental involvement is a cornerstone of PL 94-142 (Education of the Handicapped Act) in establishing parental rights in educational programming, but it has also been of concern to those who believe the natural home is the most desirable placement and would be possible for many more developmentally disabled clients if adequate services were available to the parents. These policy directions were charted often in the absence of empirical data, and research must clarify the conditions where community placement is advantageous and which conditions and for what families in-home placement is possible. Priority areas for research are the study of adjustment and psychological growth of mentally retarded people in the various residential alternatives and the adjustment of and services available to their families and care providers.

A number of questions need empirical study in order to address the question of optimal environmental influences on the mentally retarded. For example, some research now suggests that the "smaller is better" notion is not necessarily true. There may be optimal sizes for community residential facilities that interact with the nature and degree of disability to insure sufficient numbers of clients to permit friendships to be possible yet to retain the personal warmth more possible in a community residential facility. Further, we do not understand the determinants of adjustment and growth sufficiently well to recommend whether training and characteristics of staff are more or less important than characteristics of the clients in determining what kind of growth can be expected.

Research in the 1950s and 1960s sought to uncover those family/child factors associated with the decision to seek institutional placement for their mentally retarded child. In light of the trend to recommend in-home placement whenever possible, the need exists to uncover those factors associated with the ability and/or predisposition of natural parents to retain their mentally retarded child in the family. The outcomes of interest would include adjustment and psychological growth of the mentally retarded child, the adjustment and psychological growth of non-retarded siblings in the family, marital integration and/or the stress placed on the nuclear family, and the life expectancy of the child.

Increasingly in our society, single parent homes are responsible for the rearing of children. Does the single parent experience more stress due to the inability to share responsibility? If so, does this stress give rise to a greater frequency of abuse to the MRDD child in a single parent home? What kind of services are necessary in order for the single parent to keep their child in the home? With the stress of a MRDD child there is a higher divorce rate, and it would be important to study the adjustment of the MRDD child to the divorce.

The research suggested must accommodate the complexities of the family and recognize that the mentally retarded child, non-retarded siblings, and family pass through stages variously defined in terms of age, age of oldest child, age of youngest child, age of parents, or developmental tasks of children. Life expectancy of the child is very important in terms of family planning for the retarded individual. While life tables exist for institutionalized populations, few studies have examined community mortality for retarded people, with possible exception of children with Down syndrome. Institutional mortality data suggest a very short life span for some children and close to normal life expectancy for others. However, at this time definitive studies do not exist on life expectancy in the community and on whether or not remaining in the community improves longevity.

These issues require retrospective and prospective studies on a longitudinal and semi-longitudinal basis. The sequence should be:

- o Descriptive studies to describe characteristics of the mentally retarded child and his/her family related to the decision to keep the child in the home
- o Correlational studies of a retrospective nature to begin to address the question of which families should (as opposed to do) keep the child in the natural home
- o Naturalistic experimental studies which prospectively attempt to predict successful outcomes for child and/or family based on significant variables uncovered in the correlational studies.

Thus far research has been concerned primarily with infants and young children. There is an additional need for research in natural settings to address the ever changing needs of the mentally retarded and the contexts in which they live. First, the baby boom group of individuals is now reaching the 30-50 age range and with the increased longevity of many subgroups of mentally retarded persons, there are more older retarded persons than was

formerly the case. In addition, their parents are older. While the services of the under-20 group have consisted of educational programming in large part, the needs of this older group need to be studied and service delivery matched to these needs. This suggests epidemiological research to identify whether this older MRDD group is living in the community and alternative delivery systems need to be investigated to identify how their needs can be best served. In addition, the transition from adolescence to adulthood and passage into middle age need to be studied to identify critical periods and crises that arise in the lives of mentally retarded persons making these transitions.

Monitoring the Prognosis of Mentally Retarded People in the Present System of Care. Studies on prevention and remediation of mental retardation are intimately linked to the need to monitor the prognosis of retarded people in the present system of care. The early belief that all retarded people could achieve near normal development with proper interventions generally has been contradicted by historical evidence. Hence, it is not clear today whether or not constraints on development are due solely to biological agents or a mismatch between environmental and biological factors.

We need to uncover the kinds of adjustment and psychological growth that can be expected of individuals with certain characteristics. For example, efforts to study the growth of adaptive behavior in severely and profoundly mentally retarded persons has typically reported very slow gains. It is plausible that there is some point where interventions will only be successful if extremely intense. The intervention research with "at risk" populations (e.g., Milwaukee Project, Carolina Abecedarian Project) seems to suggest that some family/child units benefit from the experimental intervention while others do not. In the name of efficiency it would be desirable to identify those factors (child, family) predictive of responsiveness to the interventions vs. those which are not.

The problem of enlightened environmentalism vs. biological determinants should be addressed by at least three types of investigations. The least costly is to take advantage of recent state information systems based on large periodic surveys of residents' competence and behavior required by state administrators for accountability and budgetary purpose. These large longitudinal data sets can be used to characterize developmental expectations for many different groups of retarded individuals in various placements and exposed to a variety of programs. Methodology currently exists to estimate life span developmental trends using repeated measures over a limited time period on large samples of people. The second type of investigation depends on more in-depth cognitive and social assessments administered over a period of time to smaller samples of individuals. The more in-depth studies can take advantage of subtle changes in cognitive structure in interaction with the etiology of the client. The third type of study continues to explore novel medical and educational interventions which at least theoretically could accelerate psychological growth for specified retarded children. In conjunction with the preceding investigations, professionals and administrators concerned with mental retardation would have some notion of the efficacy of sustained education and other interventions for particular groups of retarded clients.

Studying the Needs of Aging Retarded Individuals. The problem of aging parents and their adult mentally retarded offspring is becoming more important as retarded individuals live longer, are more likely to stay at home, and at

an older age need an alternative placement when their parents are no longer able to care for them. There is very little research on this problem. We need to encourage studies of this population and consider what their primary service needs are, what the quality of life is like, and the degree to which support services or day programs can improve the long-term situation.

The aging population of the United States, starting at the retirement age of 65 or 67, are more susceptible to chronic diseases, ailments, loneliness, and an awareness of the fragility of life than persons of younger ages. The incidences of neurological, cardiovascular and other disorders and ailments increase significantly with age. The older mentally retarded person is similarly susceptible to an increase in stress and disease, except there is reason to suspect that the more severely retarded adult experiences the onset of some diseases earlier than his or her non-mentally retarded counterpart for no other reasons than he or she is usually less alert, not as mobile, and less aware of health habits and activities.

The question that should be asked is when, from a health viewpoint, is a specified mildly retarded individual to be considered aging? What are the signs of the aging syndrome and how are they to be treated and managed with a person not likely to be self-sufficient and alert to the signs? In addition, what effect does the community movement have on older mentally retarded persons? As aging mentally retarded persons outlive their care providers--natural parents or the owner-operators of small family homes--how do they adjust to separation after a lifelong stay in their natural homes or a prolonged stay in a small family home? Answers to questions such as these are largely unknown and deserve serious study as a greater number of mentally retarded people survive to older ages.

Studies dealing with this older group of retarded people will require different methodologies regarding tests, interviews, criteria for evaluation, etc. Developmental progress and survival are likely to be less of an issue than changing demands for services and adjustment to new service systems. In addition, this group will comprise primarily severe, moderately, and mildly retarded since the life expectancy of the profoundly retarded is still limited.

Ethics and Mental Retardation

This plan would not be complete without some discussion of ethics as it relates to policy planning and research decisions in the MRDD area. Ethical concerns can be usefully grouped into two categories.

The first category consists of broad concerns about policy issues with respect to the way mentally retarded and developmentally disabled persons should be considered as members of society. These include:

- o Issues surrounding the decision whether or not to provide care for or withdraw care from handicapped newborns
- o Issues surrounding what rights severely retarded people can appropriately claim
- o Issues surrounding integration of retarded people into the community

- o Issues pertaining to the education, training, and habilitation of severely retarded people
- o Issues around the question of who should speak for mentally retarded persons
- o Issues regarding the appropriate role of the mentally retarded person in society.

The second category of issues concerns ethical considerations that enter the research and scholarly process:

- o Ethics as a stimulus to empirical research. Awareness of ethical issues and problems facing our society can spur researchers to focus on certain research topics and questions in mental retardation in the hope that scientific theory and data will help improve the quality of crucial ethical decisions.
- o The ethical implications of their empirical findings and theories. Researchers can come to recognize that much of their research is ethical on its face and draw out the ethical dimensions. Although not typically done in the published literature, such a practice would undoubtedly enhance the applicability of research findings to the world of mentally retarded people.
- o The research ethics of conducting empirical research on retardation. This is the ethical topic most frequently raised by mental retardation researchers. For example, social and behavioral scientists might investigate informed consent and other research ethics processes entailed in the conduct of clinical trials, such as the NICHD-sponsored Maternal-PKU intervention study. Similar studies might be conducted as adjuncts to many types of biomedical and psychoeducational intervention research.
- o Ethical practices in typical biomedical and psychoeducational intervention programs in the field. Examples include the study of communication and decision making in neonatal intensive care units and of decisions made in early childhood intervention programs, and the ethics of decision making at the organizational level (hospital, school system, governmental unit, research funding agency).

Ethics is not just a matter of emotion or personal preference. Reason and evidence can make a difference in ethical decision making. NICHD can help the biobehavioral research community move in the direction of establishing an ethically relevant research agenda.

Conclusions and Recommendations

The following recommendations have been developed to fill gaps and enhance existing knowledge within the areas of Family and Community.

- A. Prevention of MRDD Through Research on Family and Community Processes:
 - o Studies of intervention with high risk families.
 - o Research on non-organic failure to thrive in infancy.

- o Studies of community organization and resources in provision of services to retarded individuals.
 - o Research on creating and strengthening social networks of families with handicapped individuals.
- B. Research on Programs to Ameliorate Mental Retardation and Developmental Disabilities:
- o Studying problems of care-provider burn-out both in natural family members and in other care providers.
 - o Research on the development and evaluation of educational programs which facilitate family functioning.
- C. Research on Service Delivery Systems:
- o Research on the interface between school services for severely impaired individuals and developmental disability services.
 - o Studies of the relationships between families and service providers.
 - o Studies on the effects of deinstitutionalization on neighborhoods, natural families, social services and economic institutions.
- D. Research on Aging Retarded Persons:
- o Studies of needs of aging retarded persons living with aging parents.
 - o Research on health and disease in aging retarded persons.
 - o Studies of the effects of deinstitutionalization on the aging retarded.
 - o Descriptive studies of the aging retarded population including demographic trends.

Staff Review

The past 25 years have seen major changes in our nation's approach to the care of MRDD persons. Prominent among these changes is the shift from an orientation for provision of care in institutional settings to one of mainstreaming persons with MRDD in their families and communities. With these changes there is growing demand for expanded research concerned with the problems of adaptation to life in the community for retarded persons and their families.

With advancing research knowledge, advances in medical care, and the growth in provision of services and community education, persons with Down syndrome are living longer, have been moved into home and community care, and are engaging more broadly in the work force. For these reasons, the National Down Syndrome Congress directs attention to the Down syndrome research needs in the areas of adolescence, transitions from school to work, family adaptation to persons with Down syndrome living at home, and aging.

Reliance upon home and community care is not fully shared by other consumer advocate organizations presented with other problems. Need for regional

residential centers to manage the eating and dietary behaviors of older children with Prader-Willi Syndrome is acutely felt by their parents. The Congress of Advocates for the Care of the Mentally Retarded is concerned about mainstreaming the more severely impaired and dependent retarded persons, and it is reluctant to give up reliance on residential care. The movement of the severely impaired from residential care to community based Intermediate Care Facilities is not without problems. Concern has been expressed for the quality of care provided in these facilities and mixes of MRDD conditions involving placements of severely impaired, defenseless persons with clients exhibiting disturbed, aggressive behaviors. The foregoing suggests continuing need for research and evaluation across the continuum of care provisions for the MRDD populations. These are research needs properly addressed by NICHD and other concerned agencies.

With respect to ethics, the rapid advances occurring in biotechnology, genetic engineering, and social action programs forecast the continual emergence of new ethical issues needing examination. The NIH has recognized this need by appointing an ethicist to the staff of the NIH Clinical Center and by frequently including ethicists on Consensus Development Conference Panels. The sensitivity of MRDD Branch staff to ethical issues is reflected in the decision for NICHD to join with the John F. Kennedy Center at George Peabody College of Vanderbilt University in sponsoring the May 1985 conference at the Center entitled, "When Are Intervention Decisions for Severely Retarded People Ethical? Toward An Ethically Relevant Research Agenda."

Action Steps

- o Issue an RFA to stimulate research on families with mentally retarded members.
- o Issue an RFA on the transition between adolescence and adulthood following consultation with the staff of the Administration on Developmental Disabilities.
- o Hold a conference on the problems of the aging retarded following consultation with staff of the National Institute on Aging, NIH.
- o Bring the research issues highlighted in this section of the plan to the attention of the Interagency Committee on Developmental Disabilities.
- o Identify ethical concerns on all applications supported by the MRDD Branch, analyze their relation to the research planned, and work for satisfactory resolutions.

XIV. RESOURCE AND TRAINING NEEDS

This section of the Forward Plan has five substantive parts. The first describes the Mental Retardation Research Centers (MRRCs), supported in large part by NICHD as institutional resources specializing in research into the causes, treatment, and prevention of mental retardation and developmental disabilities. The second describes the University Affiliated Facilities, supported by a mixture of Federal and State Funds to develop interdisciplinary service training programs, several of which are associated with an MRRC. The third describes the Primate Research Centers, funded in large part by the Animal Resources Branch of the Division of Research Resources, NIH, which are potentially valuable resources for MRDD research. The fourth describes the kinds of data that are potentially the most fruitful for MRDD research, not all of which now exist in adequate form. The last part describes the research training support provided by the NICHD. The section ends, as other sections, with Conclusions and Recommendations, Staff Review, and planned Action Steps.

Mental Retardation Research Centers (MRRCs)

Two decades ago, Congress undertook a major new program to reduce the burden of mental retardation in the United States. Known as Public Law 88-164, "The Mental Retardation Facilities and Community Mental Health Center Construction Act of 1963," the Act provided for the construction of "centers of excellence for research in mental retardation and related aspects of human development." Twelve centers were built with 75 percent Federal funds and 25 percent State/local matching funds between 1964 and 1970. In accepting the construction grant awards each university agreed to devote the constructed facilities for a minimum of 20 years to research in mental retardation.

The MRRCs have studied the problem of mental retardation from the perspectives of biomedical and behavioral-social research. Center specialists include biochemists, clinicians, epidemiologists, geneticists, immunologists, neuropathologists, psychologists, sociologists, and teratologists. Within this interdisciplinary milieu each center has developed its own particular areas of expertise.

A system of Core grant support for the MRRCs was established by the NICHD in 1967 for common facilities shared by several investigators within a center, for new program initiatives, and staff recruitment. To receive core funds, the centers must periodically undergo competitive peer reviews by a special mental retardation review group that judges the overall scientific excellence of the centers, and the proper utilization of their facilities.

Core support provides center investigators with a relatively strong inducement to (1) focus their efforts on mental retardation and (2) work together collaboratively in an interdisciplinary setting. The absence of departmental barriers is one of the special advantages of the MRRCs. Within this type of interdisciplinary environment, for example, it is possible to conduct developmental studies that integrate anatomic, behavioral, biochemical, immunocytochemical, and genetic approaches. Teams of scientists can propose and carry out joint research on specific problems more easily. The cost of an individual research project is also reduced because of shared core support for heavy equipment and other high cost items.

The MRRCs can also train researchers because of their multidisciplinary approach and university affiliations. The vast majority of trainees are Ph.D. laboratory bench scientists. At the present time, few trainees are being equipped to fill the knowledge gap between the laboratory and the clinic. This role requires clinical investigators who are leaders in dissemination.

University Affiliated Facilities (UAFs)

The same Congressional Act (P.L. 88-164) that established the 12 MRRCs also led to a nationwide network of university affiliated interdisciplinary training programs centered on models of service. This network now comprises 47 UAFs and 5 satellites, 16 of which receive substantial grants from the Maternal and Child Health Division (MCH), HRSA, and also from the Administration on Developmental Disabilities (ADD) of the Office of Human Development Services. Ten of these UAFs are closely affiliated with MRRCs.

The basic mission of the UAFs as defined by MCH is interdisciplinary training for persons concerned with developmental disabilities and mental retardation and the demonstration of exemplary services for persons with such disorders. Trainees receive instruction from faculty affiliated with neighboring universities and participate in programs offering direct client services.

The UAFs generally offer comprehensive services in a broad clinical setting. Involved in the process are trainees from a variety of disciplines including medicine, nursing, nutrition, dentistry, education, speech pathology, audiology, physical therapy, occupational therapy, and social work. Specific populations served include chronically ill children, the elderly, mentally retarded mothers, and patients with chromosome disorders such as Down Syndrome. Data on these special populations have not been kept systematically. As noted subsequently in this report, data bases have been developed for computer storage of client information in the field of developmental disabilities, however, diagnostic categories have not been standardized and there is no uniform reporting system for use by the UAFs.

Research is not presently an important priority of the UAFs. The ADD guidelines encourage development of a research and evaluation capacity within the UAFs. However, MCH guidelines focus on training, acknowledging in its description of standards for UAFs only that it should provide "information on the needs for further service-related research" and that it should disseminate "... research information."

A long range task force on UAFs reported 10 years ago that "it is desirable that there be as much cooperation and collaboration as is feasible between UAFs and research centers." However, close integration of the UAFs and MRRCs in the area of research has not materialized and the research potential of the UAFs is not being utilized.

Primate Center Resources for Mental Retardation Research

The Animal Resources Branch of the Division of Research Resources (DRR), NIH funds the core grants of seven Regional Primate Research Centers and provides funds to the Caribbean Primate Research Center in Puerto Rico. Major goals of the primate center program are to (1) provide high-quality animals for research, (2) identify and develop primate models of important human health

problems, and (3) develop breeding colonies so that more animals do not have to be imported from their natural habitats.

The primate center resource is potentially very valuable with respect to problems involving prevention of mental retardation. Nonhuman primates, being similar to humans in anatomy and physiology and in exhibiting complex social and cognitive behavior, offer the possibility of testing prevention techniques before they are applied to people. The primate center program already includes sophisticated research in cytogenetic and immunogenetic abnormalities, reproductive physiology and factors underlying poor pregnancy outcomes, and basic processes of physical, neural and behavioral development. Unfortunately, only a few of these primate models have been studied systematically in relation to specific issues concerning mental retardation.

One example of a naturally occurring primate model is the XXX trisomy and mosaic pigtailed macaques identified at the Washington Regional Primate Research Center. These monkeys were karyotyped after observing highly deviant neonatal development. Subsequent studies showed these animals to be mentally retarded, with physical disabilities and motor handicaps. Some parents of the animals have produced more than one karyotypically abnormal offspring. This model could be used to study effects of genetic engineering techniques on anatomy, physiology, and behavior, and the specific processes of fetal development produced by such genetic abnormalities.

Data Bases

There are two basic types of data collection: one-time measurements (cross-section data) and repeated measurements of the same entity over time (longitudinal data). Cross-section data are less time consuming to collect and much less expensive to store, process, and analyze. For these reasons, the data bases used in MRDD research have typically been cross-sectional. However, for studies of human development longitudinal data are essential because in many dimensions development is not linear and the interactions among different contributing factors are important and change over time. These interactions and changes cannot be identified by studying even large samples of children at one point in time.

As recently as 10 years ago, less than 5 percent of published studies of child development included longitudinal data. Yet many of the important theoretical contributions have been made through studying (albeit small) samples of children over time. Recently longitudinal studies have become more common, often sponsored in institutional settings such as the MRRCs where the possibility of long term support can provide appropriate conditions for carrying on multiyear projects.

It should be noted here that in principle one has the choice of retrospective versus prospective longitudinal data collection strategies. The former identifies children as, for example, mentally retarded and builds their history backward. This strategy has the obvious drawback that it will always miss children who would have appeared retarded earlier but at the point of data collection do not perform at a retarded level. Missing such observations has the danger of leading not only to partial theories but to seriously misleading ones. Only by identifying youngsters "at risk" and following them forward can we observe the interacting variables that influence some children

to develop mental retardation or developmental disabilities and others to remain free of them.

A more limited prospective approach, that is considerably less costly for a given sample size, is to study critical transition points during which the individual experiences major changes in their life environment and in the expectations of those around him. One of the least studied transition points occurs when the retarded individual leaves the public school programs or the institution and enters the work force or community. Another transition point of significance comes when the retarded child leaves the relatively protected environment of a special preschool program and faces the demands and requirements of public school.

In the field of mental retardation, several different types of data bases presently exist. They include data banks at MRRCs and UAFs, statewide systems, and special studies. They are created to maintain clinical records, chart the progress of interventions and for longitudinal studies. They usually have individual name-linked records and allow for research on process and across time. Some are amenable to questions of psychological and social development, others allow for the description (and possible evaluation) of services provided or interventions presented. They are computer based since the amount of information gathered is substantial, and the needs for access are varied, requiring a complex and flexible index that will provide retrieval.

A survey of computerized mental retardation/developmental disabilities data systems issued in December, 1980 by the Ad Hoc Committee on the Use and Construction of Data Banks (AAMD) and Data Banks Committee of the American Academy on Mental Retardation listed 70 such data banks. However, problems with them are substantial, including lack of a standard taxonomy for diagnostic categories and for services, inaccuracies in data, and varying purposes. Thus, they cannot at present be used in the aggregate as a resource from which objects of study could be drawn.

Research Training

The NICHD has a long record of supporting scientific training in the field of mental retardation and developmental disabilities. The cadre of research scientists emanating from training programs sponsored by the NICHD have been seminal in the production of research and in research leadership in this field. Any major publication in the field will cite scholarly contributions by former recipients of NICHD training support or by those who have benefited in some way from NICHD-sponsored training.

A substantial proportion of our population suffer from handicaps that affect development and intellectual functioning. Yet the number of scientists committed to research in these areas are small, as reflected not only in the number of professionals committed to the area but also in the number of students applying for research training in the field. This is particularly true for mental retardation and learning disability, which traditionally, has been viewed as having little to offer the research scientist. This state of affairs is not due primarily to the job market. The availability of jobs in academic settings has declined in all fields, MRDD and related areas included. However, the nonacademic market place in MRDD is rather robust. Graduates of MRDD programs with the Ph.D. continue to find positions

appropriate to their training. Many of these positions are in field settings such as residential institutions for the retarded, public schools, and clinics that may require some clinical duties. Most of these afford the opportunity to pursue research interests, and a review of research reported in journals suggests that a substantial proportion of it continues to derive from these field settings.

Sponsored research in MRDD does attract investigators, but many of these do not continue their interest after the grant period. Moreover, their interest in MRDD is often ancillary, concerned with research issues other than those central to remediation of intellectual handicap. Only through training that results in career-long commitments can we expect to foster the interest, dedication, knowledge, and skills necessary for a durable systematic research effort in this neglected area. In this connection, it is important to note that the number of investigators in the field is declining as measured by frequency of publications in the central journals in the field. Most current MRDD research is being produced by older researchers, with only a trickle of young investigators publishing regularly in the area.

Conclusions and Recommendation

1. Mental Retardation Research Centers (MRRCs)

Nearly two decades have passed since the original construction grants for the 12 MRRCs were awarded. Although the MRRCs have made many gains in the field of mental retardation, much remains to be learned. The causes of fully one-third of all mental retardation are still unknown. The research required to identify and map etiologies cannot be undertaken by a single investigator working alone. The complexity of modern methodology and the problems themselves necessitate a team approach. By virtue of their organizational structure, funding mechanisms, staffing patterns, and mission orientation, the MRRCs are well-suited to foster this type of research.

To take full advantage of the MRRCs, the following recommendations should be considered:

- o The Center Core funding levels authorized by congress for FY 1984 (\$8 million), FY 1985 (\$9 million) and FY 1986 (\$10 million) should be accepted by the NICHD and fully utilized by the 12 centers.
- o The universities housing the MRRCs should be encouraged to continue their commitment to mental retardation research beyond the 20-year period required at the time of acceptance of the construction grant awards through continuation of the Core grant program.
- o Funding levels for Core grant awards have traditionally been based upon the amount actually expended by a center in the prior year. The funding level recommended by the MR Research Committee should also be taken into consideration.
- o In appointing individuals to the NICHD MR Research Committee, priority consideration be given to individuals with experience in mission-oriented multidisciplinary collaborative research, and the committee should include members with a background in MRRC-based research.

- o Centers should be permitted to use a specific proportion of Core funds for staffing; not only to replace former staff who have left the MRRC but also to attract researchers who enable the center to develop in new and desirable program areas.
- o A 10 percent supplement should be added to Core grant awards for centers with a formal three- to five-year training program for clinical investigators. Furthermore, the NICHD should declare clinical investigators in mental retardation as a specific shortage area so that the MRRCs can be eligible for Institutional National Research Service Awards (T32). In addition, applications from the MRRCs for the new NIH-sponsored Physician Scientist awards should be encouraged. Also, to interest students in careers in clinical investigation, the MRRCs should be permitted to receive NRSA Professional Student Short-Term Research Training Grants (T35).
- o The NICHD should establish a set of goals for mental retardation research to which it will give priority because they are deemed socially desirable. An identified amount of extramural research funds should be set aside for proposals that address these goals but whose priority scores are outside the current funding level of grants already reviewed by NIH study sections. Recommendation to fund these grants should be made at the MR Branch level and reviewed by the National Advisory Child Health and Human Development Council (NACHHD). A mechanism should be set up for similar fund and contracts.
- o A funding mechanism needs to be developed that will enable investigators located at different centers to interact with one another on a more regular basis to develop joint proposals.

2. University Affiliated Facilities (UAFs)

As noted, the research potential of the UAFs has not been utilized to date. Surveys of the special populations that pass through the UAFs would be extremely useful to public policy makers and are within the capacity, although not the current budgets, of most UAFs. New sources of support are necessary for this research potential to be realized.

The NICHD should provide categorical research support for qualified investigators in a UAF or working in collaboration with a UAF. Priority areas include:

- o Development of uniform reporting systems for clients with developmental disabilities.
- o Surveys of medical, education, and social needs of these clients.
- o Development of evaluation instruments for service delivery programs.
- o Development of public programs for the prevention of mental retardation.

The Division of Maternal and Child Health and the Administration on Developmental Disabilities should be encouraged to support research training as part of the total training received at UAFs. In addition, training for

clinical research at the doctoral level should be encouraged by the award of stipends by the NICHD to individuals matriculating in a joint UAF-MRRC program for clinical investigators.

3. Primate Research Centers

In light of the potential importance of primates for studying specific conditions leading to mental retardation and for developing prevention techniques, the NICHD should conduct liaison with appropriate staff from the Animal Resources Branch. The purpose of this would be to identify especially valuable Primate Center resources, and to facilitate their use in mental retardation research by scientists already in the Primate Centers and others not now affiliated with a Primate Center program.

4. Data Bases

There is a need for a conference to bring together experts to exchange state of the art information on the validation and utilization of large, longitudinal data bases in scientific research on human development, with special emphasis on their use in the study of developmental and chronic disabilities. The time is particularly propitious for such a conference because of the convergence of several long-term factors:

There is increasing availability of large, longitudinal data bases on human subjects. The data collected by agencies is becoming increasingly sophisticated and detailed. Since there is increasing resistance to the use of traditional experimental designs on human subjects, there is a serious need to explore alternative approaches which can address important questions about human development. The increasing cost of collecting raw data and creating data bases specifically for individual, large-scale projects requires development of alternative techniques which can make use of the relatively lower cost of utilizing existing data sets or data being collected as part of ongoing agency operations. Computers are now being widely used by human service agencies. This proliferation means that information is frequently directly accessible on tape or disk. Recently, statisticians have developed increasingly sophisticated models for analyzing longitudinal, panel data, and dealing with quasi-experimental designs (see further below). These models are useful in overcoming some of the weaknesses of such designs. Finally, researchers now have generally available large-scale computers capable of handling huge quantities of data. Hence, more and more scientists have the interest and facilities needed to study large data bases.

The increasing availability of large, longitudinal data bases collected in natural social settings provides the opportunity for researchers to introduce something like experimental design into data analysis. Frequently, the researcher knows the "when" and the "to whom" of measurement but lacks full control over the scheduling and randomization of experimental stimuli which make a true experiment possible. Such studies have been labeled "quasi-experimental designs." It is crucial in such quasi-experimental designs that researchers be fully aware of threats to internal and external validity and to alternative interpretations of findings. The proposed conference would address some of these concerns and would present the most current thinking on how threats to internal and external validity can be estimated and minimized.

The NICHD is a good candidate to play a leadership role in the review of national data base capabilities by establishing a committee of officials from

concerned federal agencies to study and coordinate data base development and utilization. Specific steps include:

- o Setting up a contract program to provide a start for the studies and committee work.
- o Setting up, after 2-3 years, a grants program to stimulate secondary analyses of data from data bases and databanks, allowing some of the grants to be used for dissertation research.
- o Establishment by MRRC Directors of a standing committee on research-oriented data bases that may include but go beyond the state systems. This group would encourage as many research projects as possible to set up public use tapes of their data and would develop research support programs across the MRRCs and UAFs.
- o Establishment by UAF Directors of a committee on clinical data bases to set up standard formats and types of data in order that integrated clinical research and evaluations can be done across a network of such centers.

5. Research Training

In view of the obvious cost effectiveness of research training, the leveling trend in research productivity in MRDD, the diminishing numbers of new investigators entering the field, the difficulty in retaining researchers for this area, and the urgent need for new knowledge which is essential for remediation of the major social problem of MRDD, the priority for research training support should be increased. Advances in prevention and remediation will be determined by the number of well-trained research scientists who make long-term career commitments to this field.

Accompanying this increased emphasis, since the ultimate goal of NICHD with respect to MRDD is "to conduct and support research and training" relating to mental retardation and other areas, NICHD should undertake an intensive study of the relative effectiveness of its extramural research and training programs in MRDD. The specific aim of the study would be to determine the cost effectiveness of the various programs, with research productivity as the dependent variable measured by type and quality of publications. The study should include an analysis of Institutional Training Grants (T32s), Postdoctoral Fellowships (F32s), Senior Fellowship (F33s), Research Career Development Awards (K04s), New Investigator Awards (R23s), Research Project Grants (R01s), Program Project Grants (P01s), and Research Center Grants (P30s). Since the initiation of most of these programs some 20 years ago, enough data have accumulated for a definitive assessment of their effectiveness.

There are currently 12 grants, supporting 32 biomedical and 49 behavioral trainees. This balance between the two areas seems appropriate, but the number of grants should be doubled. By increasing the number of these programs, rather than their size, recruitment can be facilitated by attracting students from local and regional groups. Potential students can be recruited from the university with the research training program or from other institutions in the area. The academic emphasis in a particular program

should reflect the strengths of the department to the extent feasible within the important requirement that a program be multidisciplinary.

In addition to direct effects, there are many indirect benefits of a training grant. A funded training program calls attention to the problem area and to the potential for research in MRDD within a department, a university, or even throughout a state or region. This increased visibility leads both students and faculty in other fields to become involved in MRDD research. Graduate courses must be included in the curriculum for training grants and invariably many graduate students outside the program participate in these courses. In terms of the numbers of persons involved, both faculty and students, the research produced by them, the stimulating effects on others to do research, and the educational experiences provided those outside the program clearly justifies heavy investment of funds. It should be noted that colleges and universities make a much greater commitment to training than to research, as reflected by indirect costs on training grants.

The allocation of funds for Postdoctoral Fellowships awarded through institutional training grants should be doubled. Currently, there are 18 biomedical postdoctoral trainees and 6 behavioral postdoctoral trainees. These fellowships should be of two types:

- o Postdoctoral support awarded along with predoctoral training grants. The typical predoctoral program with six or so trainees is an ideal setting to provide training for one or two postdoctoral fellows. Typically, the postdoctoral fellow will collaborate in an ongoing research project with one or more senior investigators. They will also be involved in the direction of trainees who are junior research collaborators.
- o Postdoctoral support for multidisciplinary training. The overall objective would not be to train physicians to be psychologists or epidemiologists nor to train psychologists or others in medicine. Instead, each discipline would acquire research knowledge of other relevant disciplines, particularly their methodological skills.

There is also a compelling need for a continuing forum on research in mental retardation/developmental disabilities. Such a forum could be provided by yearly conferences that bring scientists together, both behavioral and biomedical, who are working in areas relating to MRDD. Institutions with NICHD funded training programs would take turns serving as host, thus generating conferences in various regions of the country. These conferences would not only serve as a forum for scientists actually engaged in research, but would serve also to stimulate other researchers and students. The cost of these conferences would be modest. Travel funds should be provided for the key participants along with funds to the host institution for secretarial and similar expenses and for student travel.

Staff Review

1. Mental Retardation Research Centers

The 20-year obligation of the universities housing the MRRCs to use their constructed space for the purpose of research on mental retardation and related aspects of human development will terminate for individual centers

beginning in 1988. The MRRC Program has been the cornerstone of the national effort to combat mental retardation from its inception. MRRC contributions to the field have been extensive and have raised the quality of mental retardation research significantly from its level 20 years ago. The success of the MRRC Program commends it for continuation into future years and action steps have been taken to assure this.

Beyond their contributions to the production of new research knowledge, the MRRCs in concert with their associated UAFs or clinical services have had major impact on service delivery.

The MRRCs also engage in a range of outreach service activities including the delivery of technical assistance, design and development of models to improve service delivery, and the conduct of training programs for professionals engaged in service delivery. Core support has been a major instrument enabling the MRRCs to engage in these activities.

The NICHD has limited the provision of core support to those centers constructed under the provisions of P.L. 88-164. The completion of construction and occupancy dates for the 12 MRRCs constructed under P.L. 88-164 spanned a period of four years for all but one MRRC. Thus, their obligating use period expires over a like span beginning in 1987. The same applies to their associated UAFs which were, in most instances, constructed at the same times as the MRRCs. The expiration of these obligations, change in research needs and opportunities over the past 20 years, and press to provide equitable treatment for all research institutions with concentrations of MRDD research activity indicate the desirability of opening core grant awards to competition.

The MRDD Branch staff have, in consultation with the MRRC Directors, developed a plan for opening MRRC Core Support Awards to competition beginning in 1987. The plan calls for three MRRCs to compete each year over a period of four years. The core awards will be for a period of five years. The number will remain at the existing level of 12. The competitions will be announced by issuance of RFAs in the NIH Guide to Grants and Contracts.

2. University Affiliated Facilities (UAFs)

The initial goal of a close functional relationship between MRRCs and UAFs receiving construction grant awards has been accomplished in large measure. However, Branch staff agree that the potential of the UAFs for clinical and applied research has never been fully realized and should be encouraged.

3. Primate Research Centers

Branch staff agree that the Primate Research Centers are a potentially major resource for MRDD research which have not been adequately utilized.

4. Data Bases

The massive growth of service programs over the past 25 years has developed in the absence of plans for their systematic use as providers of data useful for planning, research, and evaluation. Effort is needed to study and review these capabilities. Branch staff will work to facilitate cooperative efforts on the part of the several concerned federal agencies, directors of developmental disability programs at the State level, and leaders of the MRRCs and UAFs.

5. Research Training

Of all activities embraced in this volume, research training is regarded by Branch staff as most critical. The number of training grants supported is declining as is the number of scientists in research training. These trends, combined with the declining numbers of investigators from the current generation, points to the urgent need to expand current research training in the area of MRDD research.

Action Steps

- o Prepare guidelines establishing the criteria for award of MRRC Core Support Grant Awards.
- o Issue RFAs announcing availability of MRRC Core Grant Awards in accordance with the proposed schedule.
- o Meet with officials of the Animal Resources Branch to explore opportunities for MRDD research using resources of the Primate Research Centers.
- o Support cooperative endeavors by MRRCs and UAFs which enhance their mutual functioning.
- o Consult with officials of ADD, NIHR, and NIMH to establish an approach to data base issues indicated in this report.
- o Convene a national conference on data bases with the cooperation of the concerned Federal and State agencies, and directors of the MRRCs and UAFs.
- o Issue a program announcement requesting interdisciplinary training grant applications for MRDD research.
- o Recommend that plans for research training in the plans for MRRC core support awards be listed as a critical element in the guidelines.

DISCRIMINATION PROHIBITED: Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee of applicant for employment because of race, color, religion, sex, or national origin. Therefore, the activities of the National Institute of Child Health and Human Development must be operated in compliance with these laws and Executive Orders.

PRESENTATION BY

DR. ANTHONY DEMSEY
CHIEF, REFERRAL AND REVIEW BRANCH
DIVISION OF RESEARCH GRANTS
NATIONAL INSTITUTES OF HEALTH
WESTWOOD BUILDING, ROOM 338
(301) 496-7023

at the

NATIONAL ADVISORY BOARD ON MEDICAL REHABILITATION RESEARCH

Meeting on

MAY 9-10, 1991

**NIH
PEER
REVIEW
OF
RESEARCH GRANT APPLICATIONS**

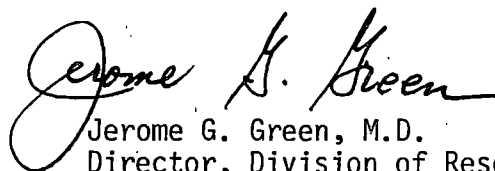
APRIL 1990

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE NATIONAL INSTITUTES OF HEALTH**

12

PREFACE

This booklet is based on a set of slides prepared by the Referral and Review Branch of the Division of Research Grants. As such, it is not intended to be a comprehensive exposition of the peer review process at the National Institutes of Health, but rather a handout to accompany lectures, slide presentations, or seminars. Extra copies of the booklet are available from the Office of Grants Inquiries, Division of Research Grants, National Institutes of Health, Bethesda, Maryland 20892.

A handwritten signature in cursive script, reading "Jerome G. Green". The signature is written in dark ink and is positioned above the printed name and title.

Jerome G. Green, M.D.
Director, Division of Research Grants

NIH PEER REVIEW OF RESEARCH GRANT APPLICATIONS

NIH

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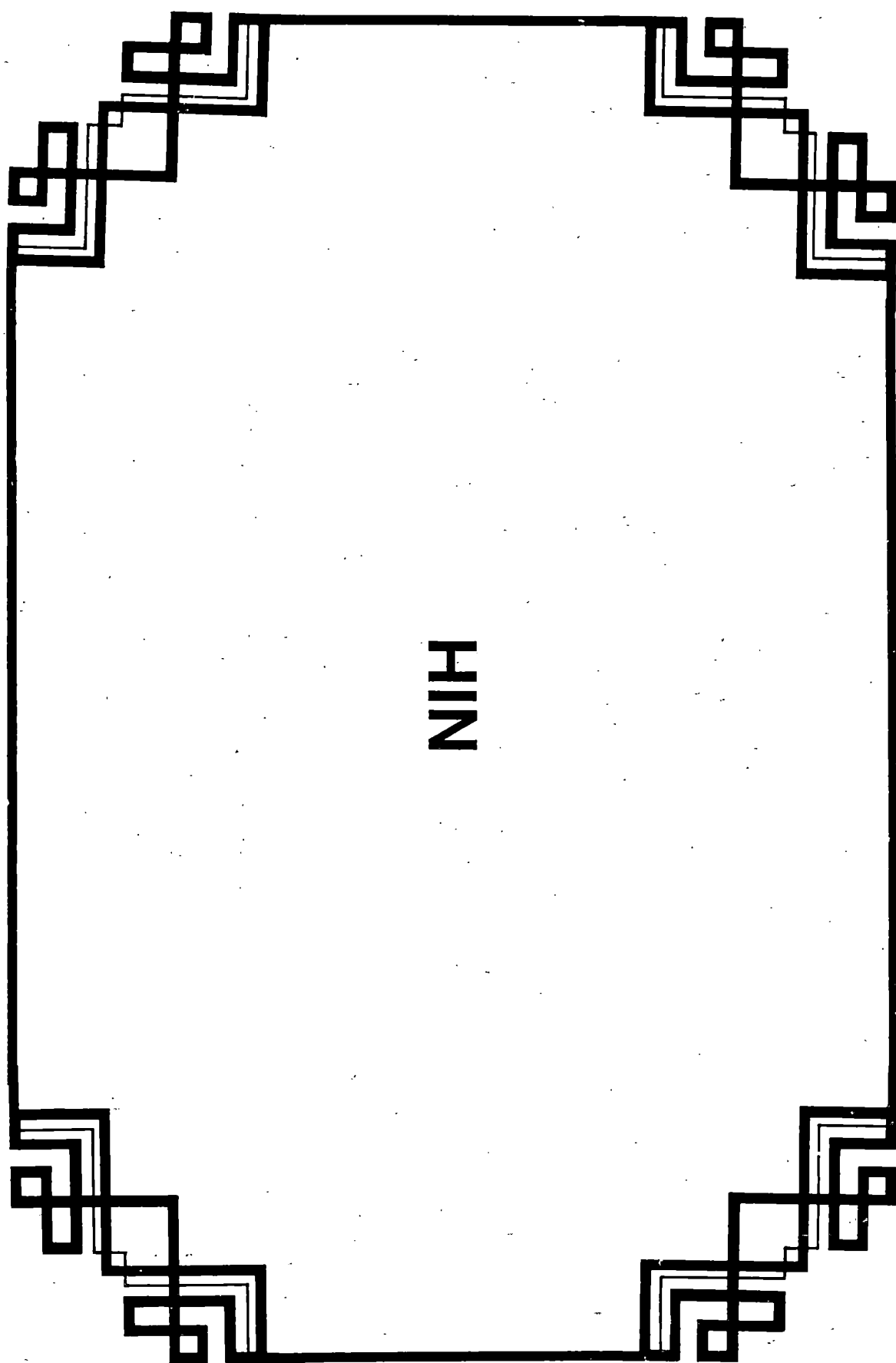
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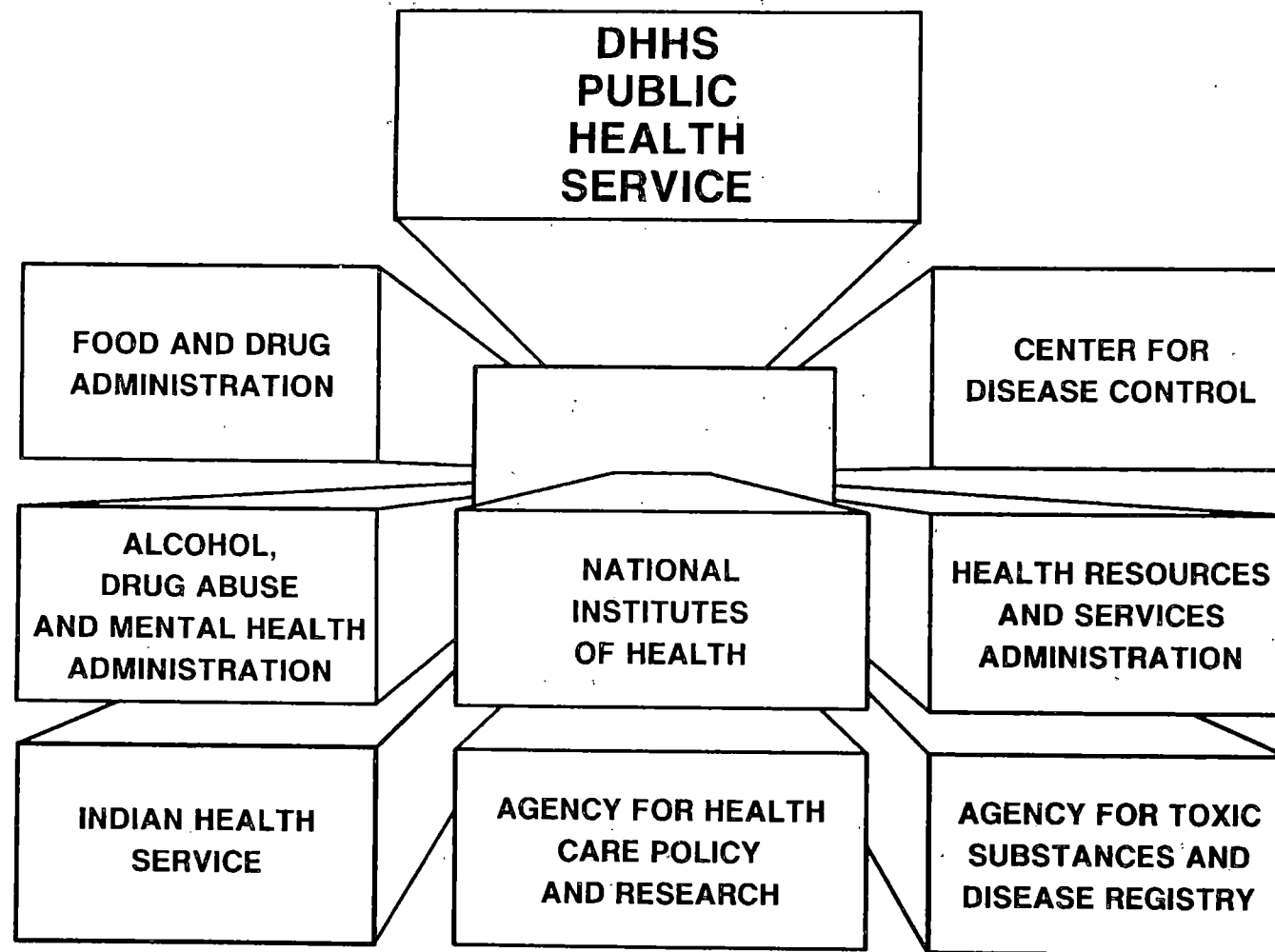
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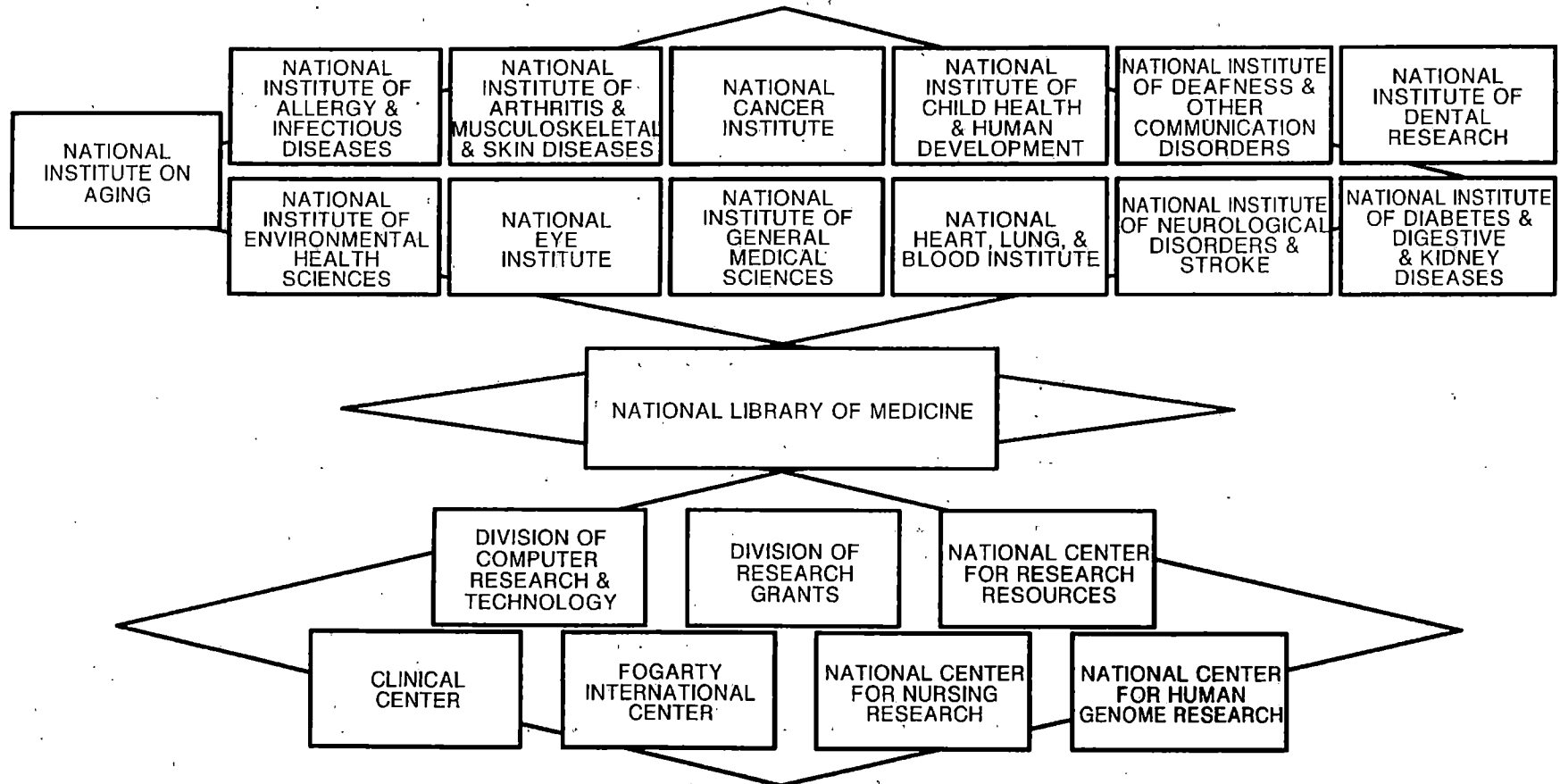


HIN

AN AGENCY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES



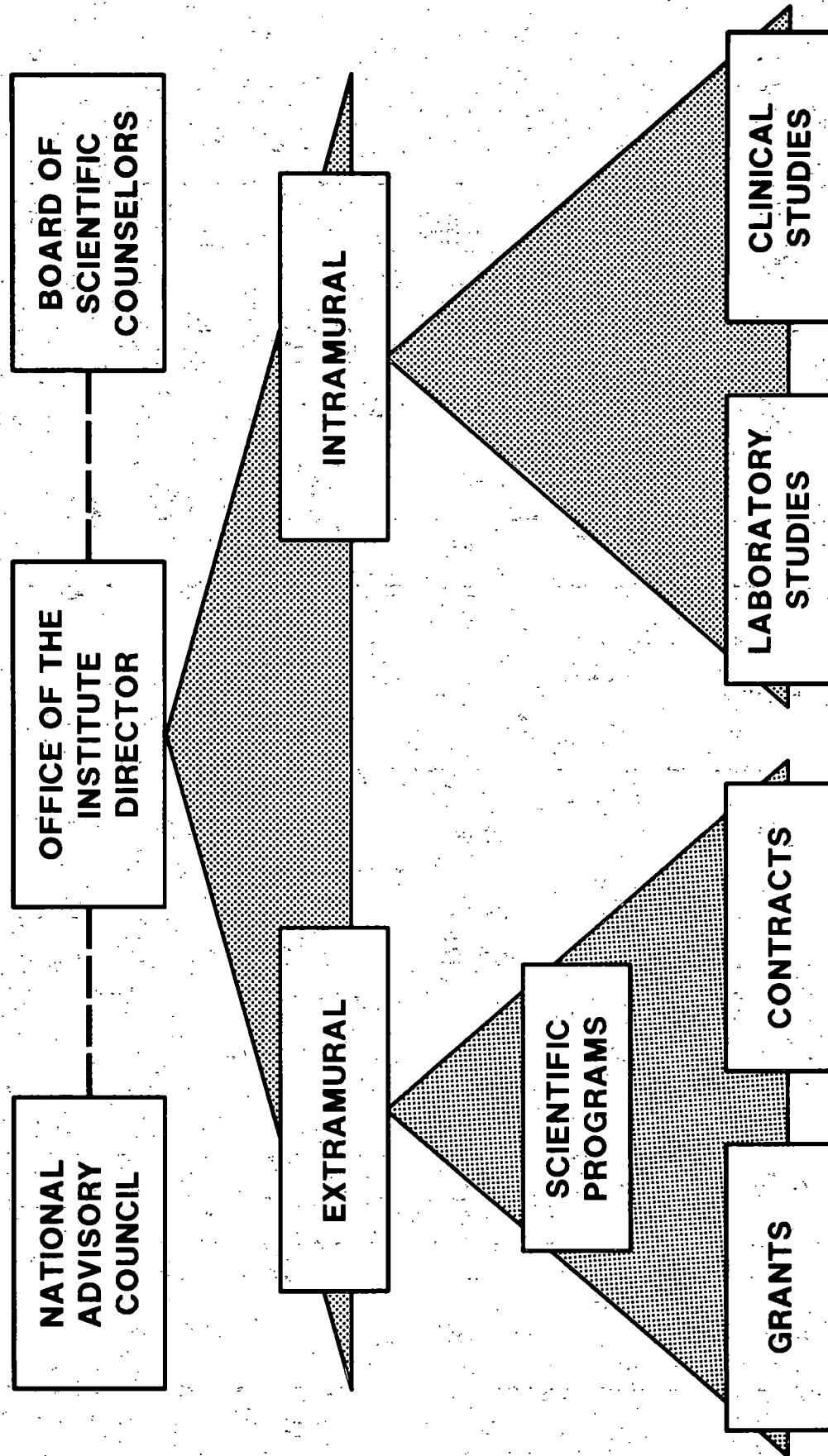
NATIONAL INSTITUTES OF HEALTH



NIH EXTRAMURAL AWARDING COMPONENTS

- **NATIONAL CANCER INSTITUTE (NCI)**
- **NATIONAL HEART, LUNG AND BLOOD INSTITUTE (NHLBI)**
- **NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES (NIDDK)**
- **NATIONAL LIBRARY OF MEDICINE (NLM)**
- **NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD)**
- **NATIONAL INSTITUTE OF DEAFNESS AND OTHER COMMUNICATION DISORDERS (NIDCD)**
- **NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS)**
- **NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS)**
- **NATIONAL INSTITUTE ON AGING (NIA)**
- **NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)**
- **NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES (NIAMS)**
- **NATIONAL INSTITUTE OF DENTAL RESEARCH (NIDR)**
- **NATIONAL EYE INSTITUTE (NEI)**
- **NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES (NIGMS)**
- **NATIONAL CENTER FOR RESEARCH RESOURCES**
- **NATIONAL CENTER FOR NURSING RESEARCH (NCNR)**
- **FOGARTY INTERNATIONAL CENTER (FIC)**
- **NATIONAL CENTER FOR HUMAN GENOME RESEARCH**

A TYPICAL INSTITUTE



NIH EXTRAMURAL PROGRAM

MECHANISM	NIH ROLE
GRANT	PATRON (ASSISTANCE, ENCOURAGEMENT)
COOPERATIVE AGREEMENT	PARTNER (ASSISTANCE BUT SUBSTANTIAL PROGRAM INVOLVEMENT)
CONTRACT	PURCHASER (PROCUREMENT)

PROGRAM ANNOUNCEMENT

- **DESCRIBES EXISTENCE OF AN NIH EXTRAMURAL RESEARCH ACTIVITY**
- **MAY DESCRIBE NEW OR EXPANDED INTEREST IN A PARTICULAR EXTRAMURAL PROGRAM**
- **MAY BE A REMINDER OF A CONTINUING INTEREST IN AN EXTRAMURAL PROGRAM**
- **HAS NO FUNDS SET ASIDE**

REQUEST FOR APPLICATIONS (RFA)

- **FORMAL ANNOUNCEMENT DESCRIBING AN INSTITUTE INITIATIVE IN A WELL-DEFINED SCIENTIFIC AREA**
- **INVITATION TO THE FIELD TO SUBMIT RESEARCH GRANT APPLICATIONS FOR A ONE-TIME COMPETITION**
- **SET-ASIDE OF FUNDS FOR A CERTAIN NUMBER OF AWARDS**

NIH GUIDE

**for GRANTS
and CONTRACTS**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

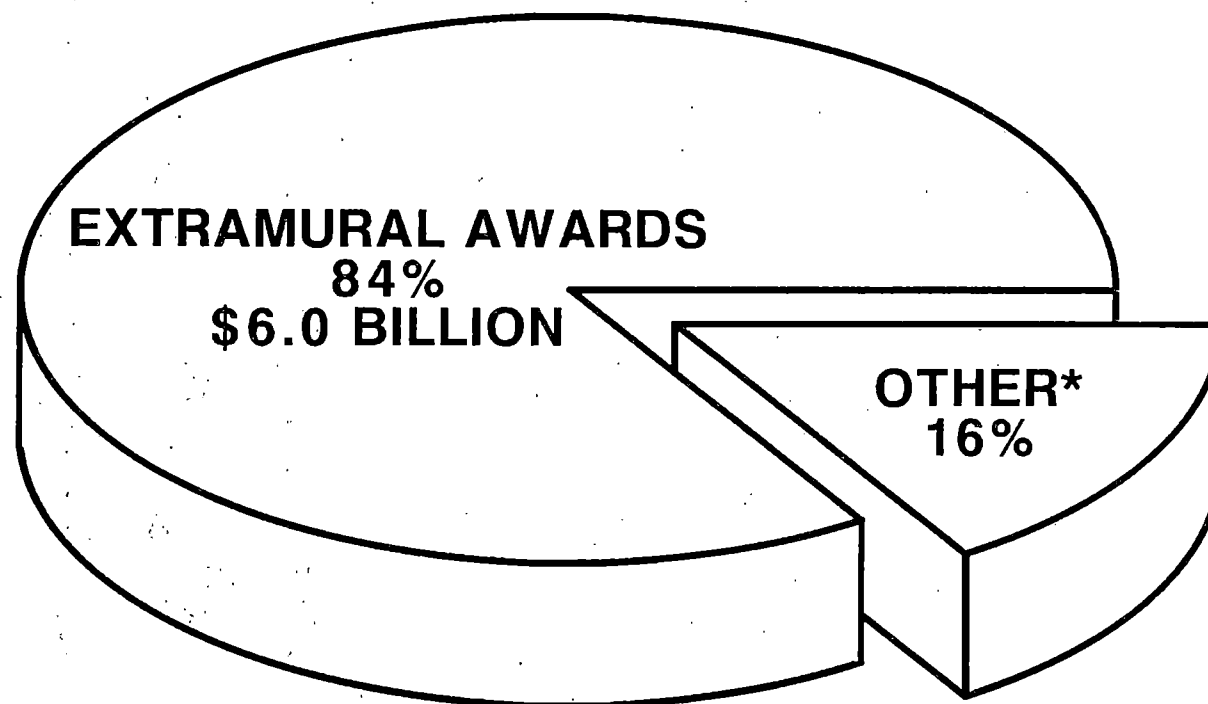
ANNOUNCES NIH SCIENTIFIC INITIATIVES

**PROVIDES NIH POLICY AND ADMINISTRATIVE
INFORMATION**

**TO RECEIVE THE NIH GUIDE FOR
GRANTS AND CONTRACTS, WRITE TO:**

**GRANTS AND CONTRACT GUIDE
DISTRIBUTION CENTER
NATIONAL INSTITUTES OF HEALTH
BUILDING 31, ROOM B4BNO8
BETHESDA, MD. 20892**

NIH BUDGET FISCAL YEAR 1989



TOTAL - \$7.2 BILLION

***INCLUDES DIRECT RESEARCH ACTIVITIES, MANAGEMENT COSTS, BUILDINGS AND FACILITIES, INTERAGENCY AGREEMENTS, ETC.**

SOURCE: NIH, DRG, INFORMATION SYSTEMS BRANCH.

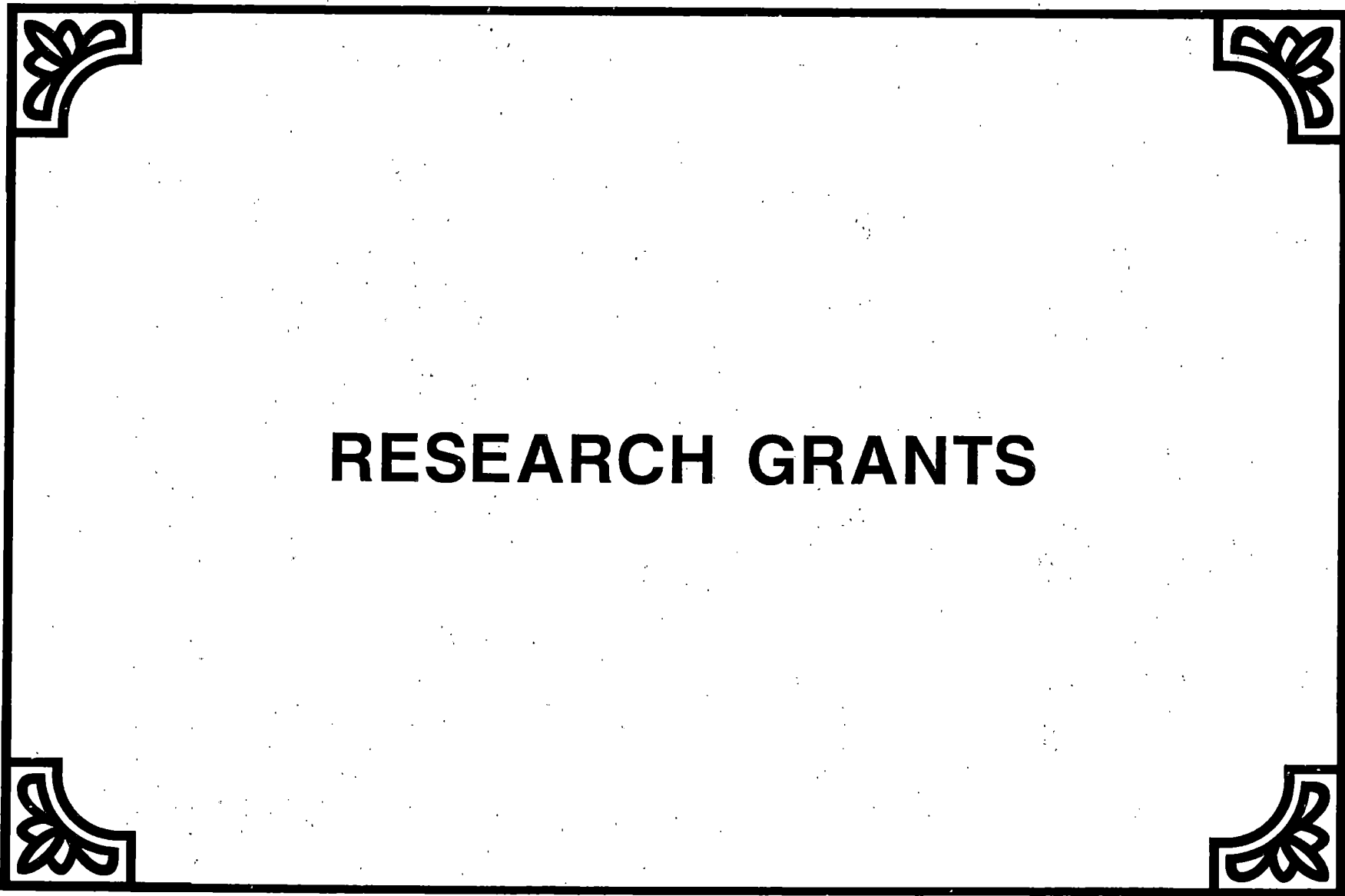
NIH PEER REVIEW OF RESEARCH GRANT APPLICATIONS

SEPTEMBER 1990

12

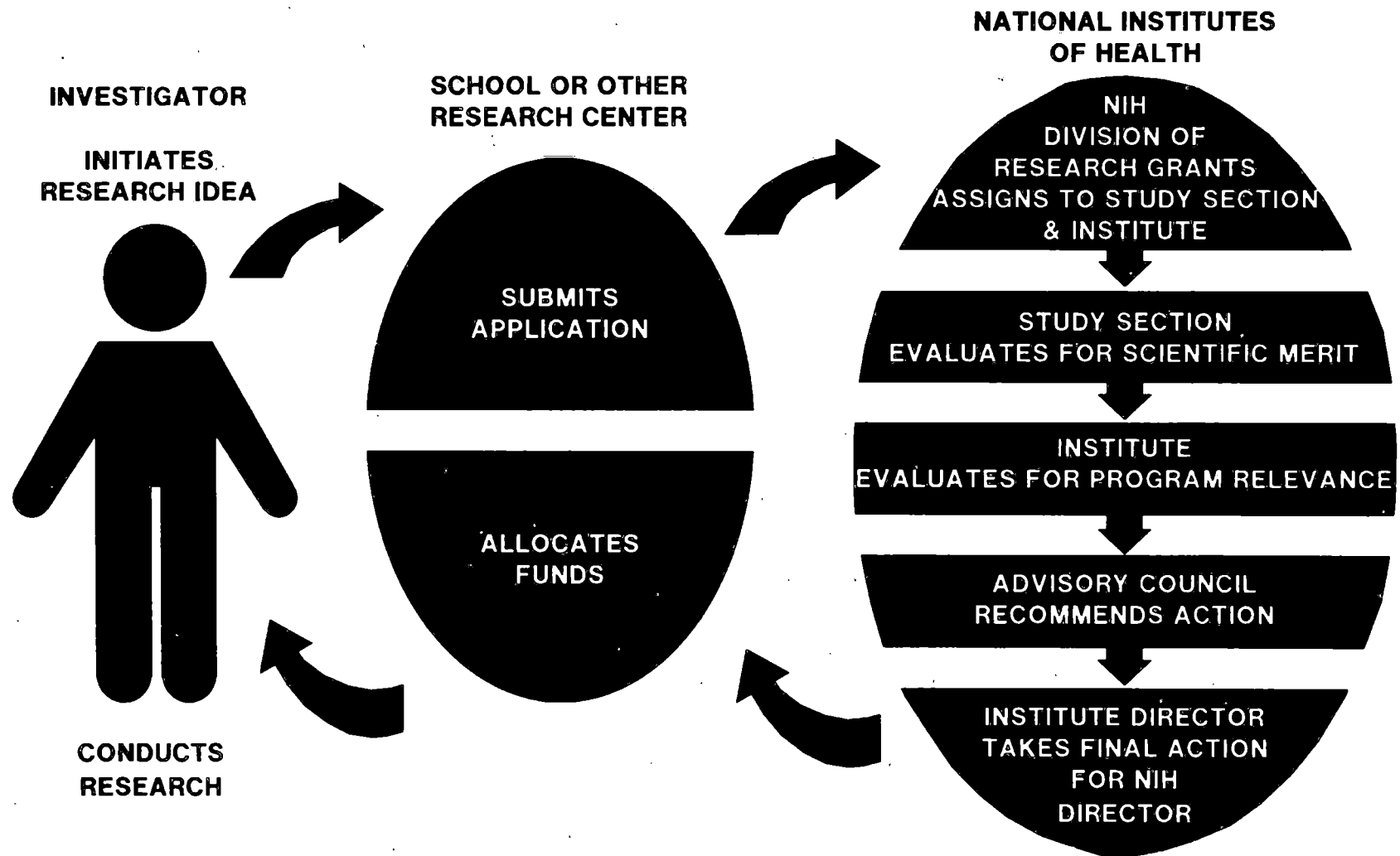
DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE · NATIONAL INSTITUTES OF HEALTH



RESEARCH GRANTS

HOW A RESEARCH GRANT IS MADE



DUAL REVIEW SYSTEM FOR GRANT APPLICATIONS

FIRST LEVEL OF REVIEW

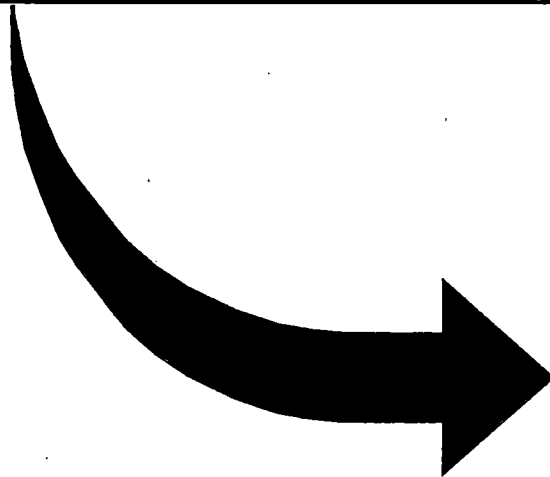
SCIENTIFIC REVIEW GROUP

- PROVIDES INITIAL SCIENTIFIC REVIEW OF GRANT APPLICATIONS
- DOES NOT SET PROGRAM PRIORITIES
- MAKES BUDGET RECOMMENDATIONS BUT NO FUNDING DECISIONS

SECOND LEVEL OF REVIEW

COUNCIL

- ASSESSES QUALITY OF SRG REVIEW OF GRANT APPLICATIONS
- MAKES RECOMMENDATION TO INSTITUTE STAFF ON FUNDING
- EVALUATES PROGRAM PRIORITIES AND RELEVANCE
- ADVISES ON POLICY



TYPES OF INITIAL REVIEW GROUPS

GROUPS

- **DRG**
 - **REGULAR STUDY SECTIONS**
 - **SPECIAL STUDY SECTIONS**

- **INSTITUTES**
 - **INITIAL REVIEW GROUPS**
 - **CONTRACT REVIEW COMMITTEES**

APPLICATIONS REVIEWED

- **RESEARCH PROJECTS**
- **FIRST AWARDS**
- **RCDAS**
- **ACADEMIC RESEARCH ENHANCEMENT AWARDS**
- **POSTDOCTORAL FELLOWSHIPS**
- **SMALL BUSINESS INNOVATION RESEARCH**
- **SHARED INSTRUMENTATION**

- **PROGRAM PROJECTS**
- **CENTERS**
- **INSTITUTIONAL TRAINING GRANTS**
- **CONTRACTS**
- **RFAS**

PEER REVIEW OF NIH SUPPORT MECHANISMS

DRG

INSTITUTES

RESEARCH PROJECT GRANT (R01) FIRST INDEPENDENT RESEARCH SUPPORT & TRANSITION (FIRST) AWARD (R29) RESEARCH CAREER DEVELOPMENT AWARD (K04) POSTDOCTORAL FELLOWSHIP (F32) SENIOR FELLOWSHIP (F33) FOGARTY INTERNATIONAL CENTER FELLOWSHIPS (F05, F06) SHORT-TERM TRAINING AWARD (T35) SMALL BUSINESS GRANTS (R43, R44) ACADEMIC RESEARCH ENHANCEMENT AWARD (R15) U.S. - JAPAN COOPERATIVE MEDICAL SCIENCE PROGRAM (R22) BIOMEDICAL RESEARCH SUPPORT SHARED INSTRUMENTATION GRANT (S10)	PROGRAM PROJECT GRANT (P01)* CENTER GRANTS (P30, P50, P60) INSTITUTIONAL FELLOWSHIP (T32) ACADEMIC AWARD (K07) CLINICAL INVESTIGATOR AWARD (K08) CONFERENCE GRANT (R13)* MARC FELLOWSHIPS (F34, F36, T34) MINORITY BIOMEDICAL SUPPORT GRANT (S06) PHYSICIAN SCIENTIST AWARD (K11, K12) RESOURCE GRANTS (P40, P41, R24, R26, R28) CONTRACT
---	--

*REVIEWED BY DRG UPON REQUEST

**RESEARCH GRANT
APPLICATION KIT
PHS - 398**

MAIL COMPLETED FORMS TO:

**DIVISION OF RESEARCH GRANTS
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20892**

APPLICATION RECEIPT DATES

JAN. 10 MAY 10 SEPT. 10	<u>ALL</u> *INDIVIDUAL NATIONAL RESEARCH SERVICE AWARD (NRSA) APPLICATIONS. <u>ALL</u> *INSTITUTIONAL NATIONAL RESEARCH SERVICE AWARD APPLICATIONS
FEB. 1 JUNE 1 OCT. 1	<u>ALL</u> NEW GRANT AND RESEARCH CAREER DEVELOPMENT AWARD APPLICATIONS. <u>ALL</u> *PROGRAM PROJECT AND CENTER GRANT APPLICATIONS.
MAR. 1 JULY 1 NOV. 1	REVISED, COMPETING CONTINUATION, & SUPPLEMENTAL RESEARCH GRANT AND RESEARCH CAREER DEVELOPMENT AWARD APPLICATIONS.
APR. 15 AUG. 15 DEC. 15	SMALL BUSINESS INNOVATION RESEARCH PROGRAM (SBIR), BOTH PHASES. (PHASE II APPLICANTS MUST HAVE COMPLETED A FEDERALLY-FUNDED PHASE I PROJECT).
JAN. 2 MAY 1 SEPT. 1	NEW & COMPETING CONTINUATION INVESTIGATOR-INITIATED ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) APPLICATIONS FOR EXPEDITED REVIEW.
JUNE 22	ACADEMIC RESEARCH ENHANCEMENT AWARD (AREA) APPLICATIONS.

*INCLUDES NEW, COMPETING CONTINUATION, SUPPLEMENTAL, AND REVISED.

NIH GRANT RECEIPT, REVIEW, AND AWARD SCHEDULE

JAN / APRIL MAY / AUG SEPT / DEC	RECEIPT DATES
JUNE / JULY OCT / NOV FEB / MAR	INITIAL REVIEW GROUP DATES
SEPT / OCT JAN / FEB MAY / JUNE	NATIONAL ADVISORY COUNCIL BOARD DATES
DEC 1 APR 1 JULY 1	EARLIEST POSSIBLE BEGINNING DATE*

***UNLESS THE SCHEDULE IS SPECIFIED DIFFERENTLY IN ADDITIONAL INSTRUCTIONS, OR A REQUEST FOR APPLICATION, OR THE APPLICATION IS TO UNDERGO EXPEDITED REVIEW CYCLE.**

WHEN PREPARING AN APPLICATION

- **READ INSTRUCTIONS**
- **NEVER ASSUME THAT REVIEWERS "WILL KNOW WHAT YOU MEAN"**
- **REFER TO LITERATURE THOROUGHLY AND THOUGHTFULLY**
- **EXPLICITLY STATE THE RATIONALE OF PROPOSED INVESTIGATION**
- **INCLUDE WELL-DESIGNED TABLES AND FIGURES**
- **PRESENT AN ORGANIZED, LUCID WRITE-UP**

RESEARCH INVOLVING HUMAN SUBJECTS

IMPORTANT CONSIDERATIONS

- **IS THE PROPOSED STUDY EXEMPT FROM HUMAN SUBJECT REVIEW?**
- **ARE THERE ANY APPARENT RISKS* TO THE HUMAN SUBJECTS?**
- **ARE THE PROTECTIONS ADEQUATE?**
- **WHAT ARE THE POTENTIAL BENEFITS TO THE SUBJECTS AND TO MANKIND?**

*** "RISKS" INCLUDE THE POSSIBILITY OF PHYSICAL, PSYCHOLOGICAL, OR SOCIAL INJURY RESULTING FROM RESEARCH.**

RESEARCH INVOLVING HUMAN SUBJECTS

AREAS EXEMPT FROM HUMAN SUBJECT REVIEW

- **NORMAL EDUCATIONAL PRACTICES**
- **EDUCATIONAL TESTS**
 - SUBJECTS NOT IDENTIFIED
- **SURVEY OR INTERVIEW PROCEDURES**
 - SUBJECTS NOT IDENTIFIED
 - SUBJECTS' PRIVACY RIGHTS PROTECTED
- **OBSERVATION OF PUBLIC BEHAVIOR**
 - SUBJECTS' PRIVACY RIGHTS PROTECTED
- **COLLECTION OR STUDY OF EXISTING DATA, DOCUMENTS, RECORDS, SPECIMENS**
 - INFORMATION PUBLICLY AVAILABLE
 - SUBJECTS NOT IDENTIFIED
- **PUBLIC BENEFIT OR SERVICE PROGRAMS, SUCH AS THOSE UNDER THE SOCIAL SECURITY ACT**

ANIMAL WELFARE

IMPORTANT CONSIDERATIONS

- **WILL THE ANTICIPATED RESULTS BE FOR THE GOOD OF SOCIETY?**
- **WILL THE WORK BE PLANNED AND PERFORMED BY QUALIFIED SCIENTISTS?**
- **WILL THE ANIMALS BE TREATED SO AS TO AVOID ANY UNNECESSARY DISCOMFORT, PAIN, ANXIETY, OR POOR HEALTH?**
- **SPECIES CHOSEN**
- **ANIMALS IN SHORT SUPPLY**

HAZARDOUS CONDITIONS

IMPORTANT CONSIDERATIONS

- **ARE THE NECESSARY SPECIAL FACILITIES AVAILABLE TO PROTECT THE ENVIRONMENT AND RESEARCH PERSONNEL FROM POTENTIALLY HAZARDOUS CONDITIONS?**
- **WILL BIOHAZARDOUS MATERIALS BE HANDLED APPROPRIATELY?**
- **HAVE EMPLOYEES BEEN TRAINED ADEQUATELY IN SAFE PRACTICES?**

NOTE: RESEARCH USING RECOMBINANT DNA TECHNIQUES MUST MEET NIH GUIDELINES AS DETERMINED BY THE OFFICE OF RECOMBINANT DNA ACTIVITIES (ORDA). STUDY SECTIONS NEED ONLY IDENTIFY THE SCIENTIFIC MERIT AND ANY BIOHAZARDS IN SUCH RESEARCH.

DIVISION OF RESEARCH GRANTS (DRG)

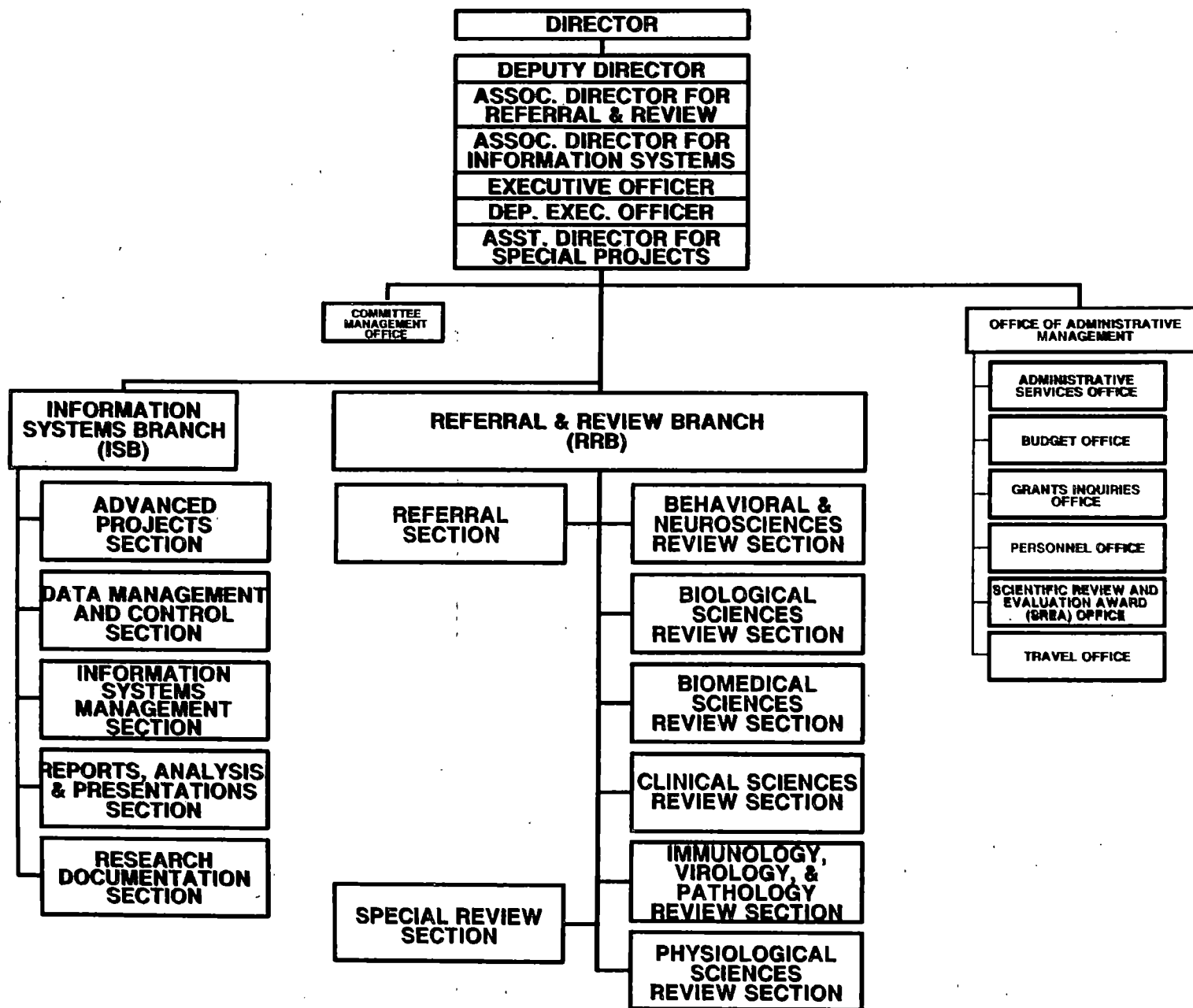
REFERRAL

- **CENTRAL RECEIPT POINT FOR PHS GRANT APPLICATIONS**
- **INSTITUTE ASSIGNMENT**
- **ASSIGNMENT TO DRG STUDY SECTION OR INSTITUTE INITIAL REVIEW GROUP**

SCIENTIFIC REVIEW

- **MORE THAN 65 STUDY SECTIONS THAT CONDUCT INITIAL MERIT REVIEW OF**
 - **RESEARCH GRANT APPLICATIONS**
 - **RCDA APPLICATIONS**
 - **POSTDOCTORAL FELLOWSHIP APPLICATIONS**
 - **FIRST AWARD APPLICATIONS**
 - **ACADEMIC RESEARCH ENHANCEMENT AWARD APPLICATIONS**
 - **SMALL BUSINESS INNOVATION RESEARCH GRANT APPLICATIONS**
 - **OTHER TYPES OF APPLICATIONS UPON REQUEST**

DRG ORGANIZATIONAL CHART

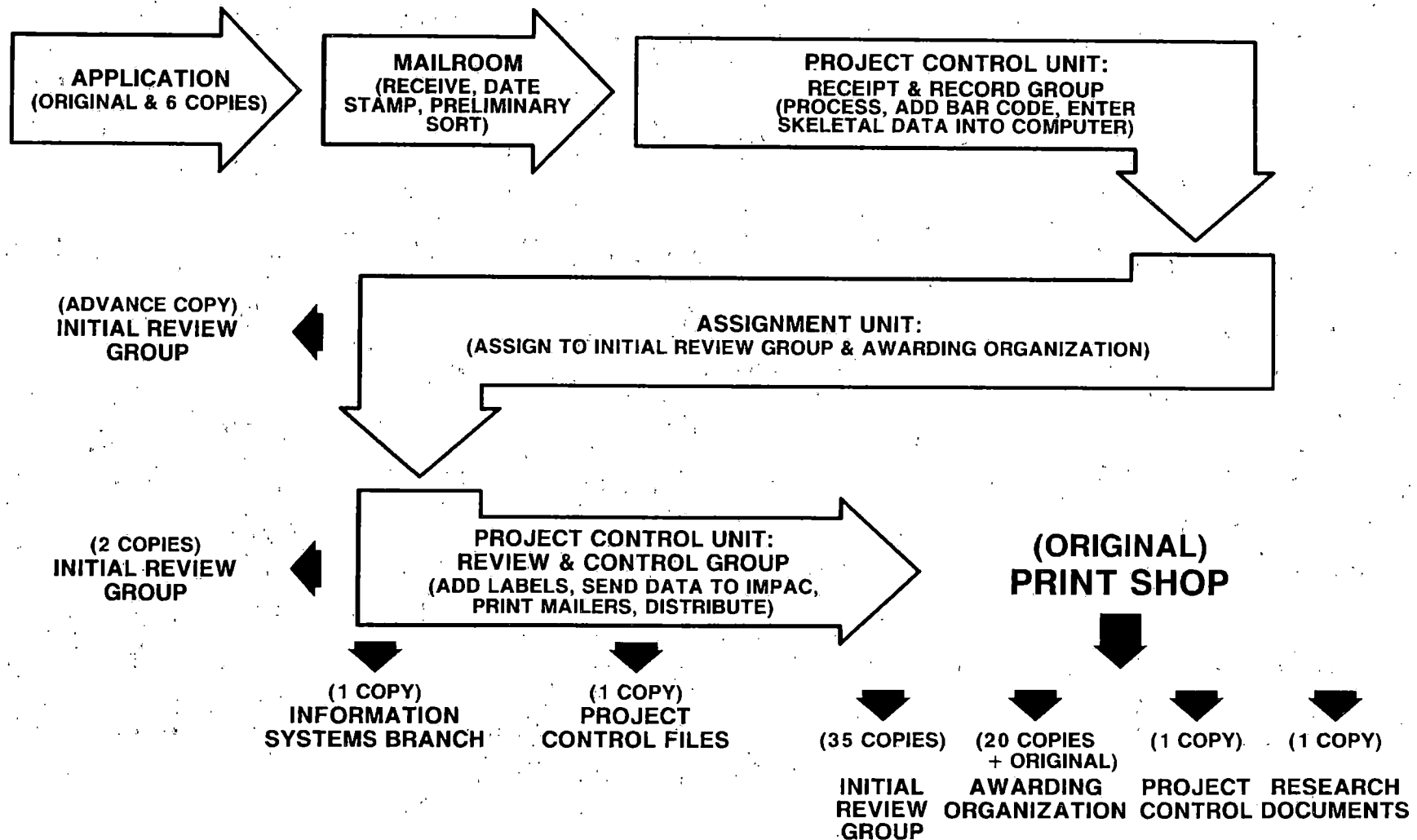


**RECEIPT AND ASSIGNMENT
IN THE REFERRAL SECTION**

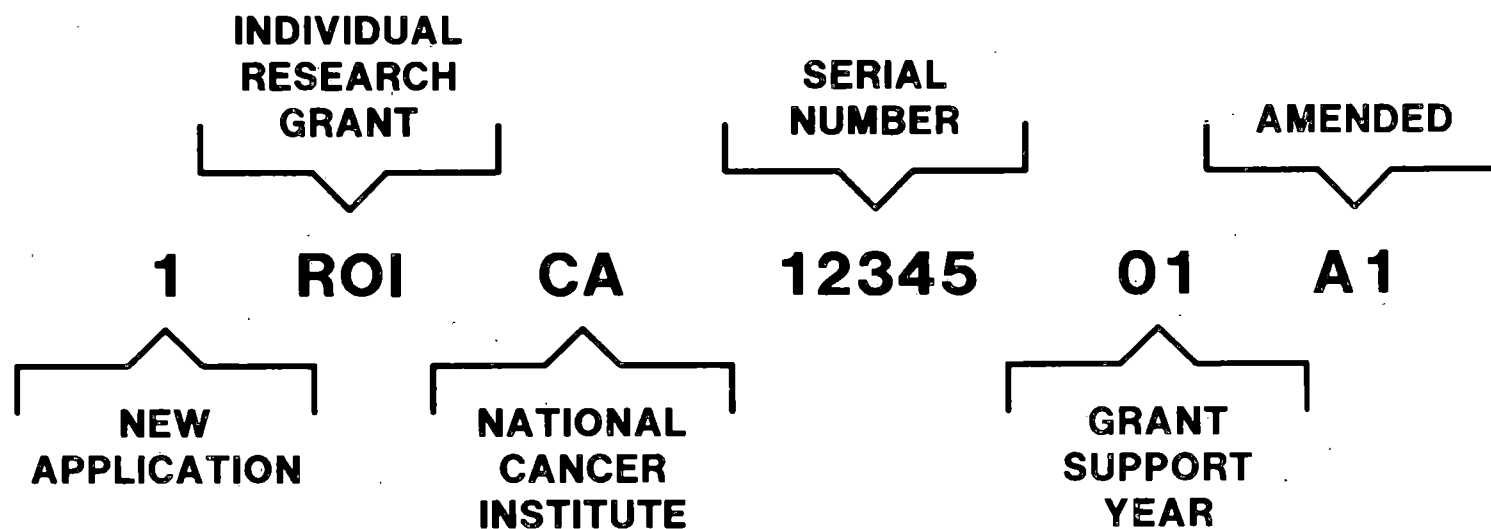
VOLUME OF COMPETING APPLICATIONS PROCESSED FOR REVIEW BY THE DIVISION OF RESEARCH GRANTS

<u>FISCAL YEAR</u>	<u>REVIEWED BY PHS</u>	<u>REVIEWED BY NIH</u>	<u>REVIEWED BY DRG</u>
1975	23,176	16,916	15,099
1980	26,396	21,105	18,661
1981	27,877	22,729	20,260
1982	26,430	23,449	20,382
1983	28,124	23,984	20,694
1984	28,724	25,358	21,824
1985	31,807	28,470	23,626
1986	30,393	26,884	22,481
1987	33,842	28,761	22,857
1988	32,771	28,888	23,089
1989	34,735	29,121	24,111

FLOW OF A COMPETING GRANT APPLICATION THROUGH THE DRG REFERRAL SECTION



SAMPLE APPLICATION NUMBER



REFERRAL NOTIFICATION (ASSIGNMENT)

F
R
O
M

IRG: (VR)
VIROLOGY SS
DR. BRUCE MAURER, EXEC. SECY.
DIV. OF RESEARCH GRANTS W/B 309
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD. 20892 (301) 496-7605

U.S. MAIL
POSTAGE & FEES PAID
U.S. DEPT. OF H.H.S.
HHS 396

02/05/88

A GRANT APPLICATION HAS BEEN RECEIVED BY NIH AND ASSIGNED TO AN INITIAL REVIEW GROUP (IRG) FOR SCIENTIFIC MERIT EVALUATION AND TO AN INSTITUTE FOR FUNDING CONSIDERATION. THE INITIAL PEER REVIEW SHOULD BE COMPLETED BY 07/88 AND (EXCEPT FOR FELLOWSHIPS) A FUNDING DECISION SHOULD BE MADE SHORTLY AFTER THE APPROPRIATE NATIONAL ADVISORY GROUP MEETS IN 10/88. FOR QUESTIONS ABOUT THE ASSIGNMENT, CONTACT THE REFERRAL OFFICE (301) 496-7447. FOR QUESTIONS PRIOR TO THE REVIEW, CONTACT THE IRG EXECUTIVE SECRETARY OR THE INDIVIDUAL LISTED ABOVE. FOR QUESTIONS AFTER THE REVIEW, CONTACT THE INSTITUTE LISTED BELOW.

PRINCIPAL INVESTIGATOR: WHITTON, J LINDSAY

TITLE: ANALYSIS OF CYTOTOXIC T CELL RESPONSE TO VIRUS INFECTION

ASSIGNMENT NUMBER: 1R01A127028-01

IRG: VR

COUNCIL: 10-88

NATL INST ALLERGY/INFECTIOUS DIS
EXTRAMURAL ACTIVITIES WW 703
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD. 20892 (301) 496-7291



WHITTON, J LINDSAY
SCRIPPS CLINIC & RES FOUND
10666 N TORREY PINES ROAD
LA JOLLA, CA 92037

ASSIGNMENT OF APPLICATIONS

● REVIEW GROUP

● INSTITUTE

Form Approved Through 9/30/89
OMB No. 0925-0001

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE



47166

GRANT APPLICATION

FOLLOW INSTRUCTIONS CAREFULLY

NAME: SMITH, BRIAN E
APPL NO:1 RO1 A154321-01
DUAL:
IRG:GEN

COUN DATE: 05/88
RCVD:09-15-87

1. TITLE OF PROJECT (Up to 56 spaces)

Genetic Basis for Cyclosporin Activity

2. RESPONSE TO SPECIFIC PROGRAM ANNOUNCEMENT ☒ NO ☐ YES (If "YES," state RFA number and/or announcement title)

3. PRINCIPAL INVESTIGATOR/ PROGRAM DIRECTOR

NEW INVESTIGATOR ☐

3a. NAME (Last, first, middle)

Smith, Brian E.

3b. DEGREE(S)

Ph.D.

3c. SOCIAL SECURITY NUMBER

111-11-1111

HOW ARE ASSIGNMENTS MADE?

TO STUDY SECTIONS BASED ON:

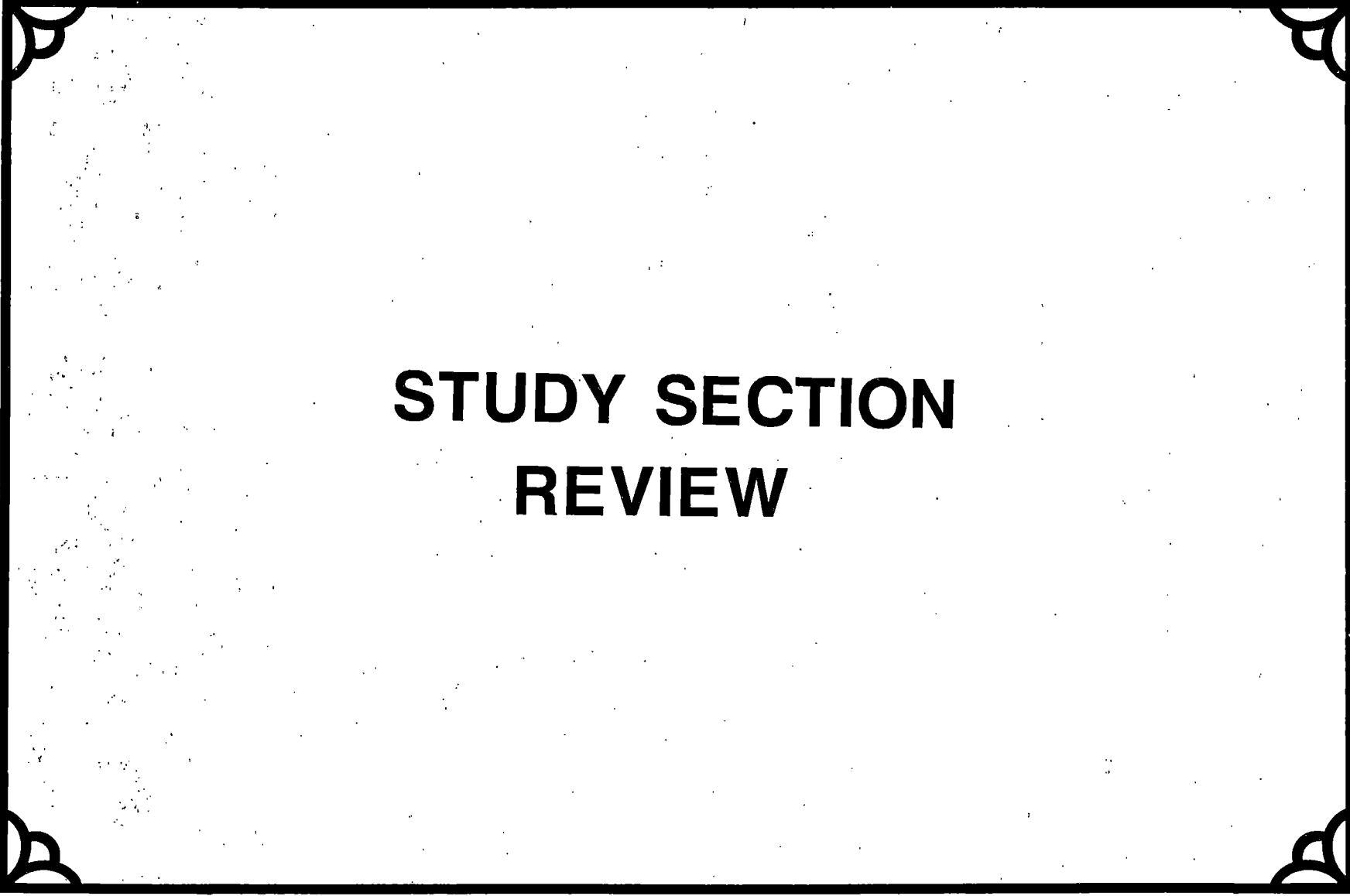
- **SPECIFIC REVIEW GUIDELINES OF EACH STUDY SECTION**

TO INSTITUTES BASED ON:

- **OVERALL MISSION OF THE INSTITUTE**
- **SPECIFIC PROGRAMMATIC MANDATES AND INTERESTS OF THE INSTITUTE**

WHO ASSIGNS APPLICATIONS

- **REFERRAL OFFICERS -- PROFESSIONAL SCIENTISTS MOST OF WHOM ALSO SERVE AS EXECUTIVE SECRETARIES OF DRG STUDY SECTIONS**



STUDY SECTION REVIEW

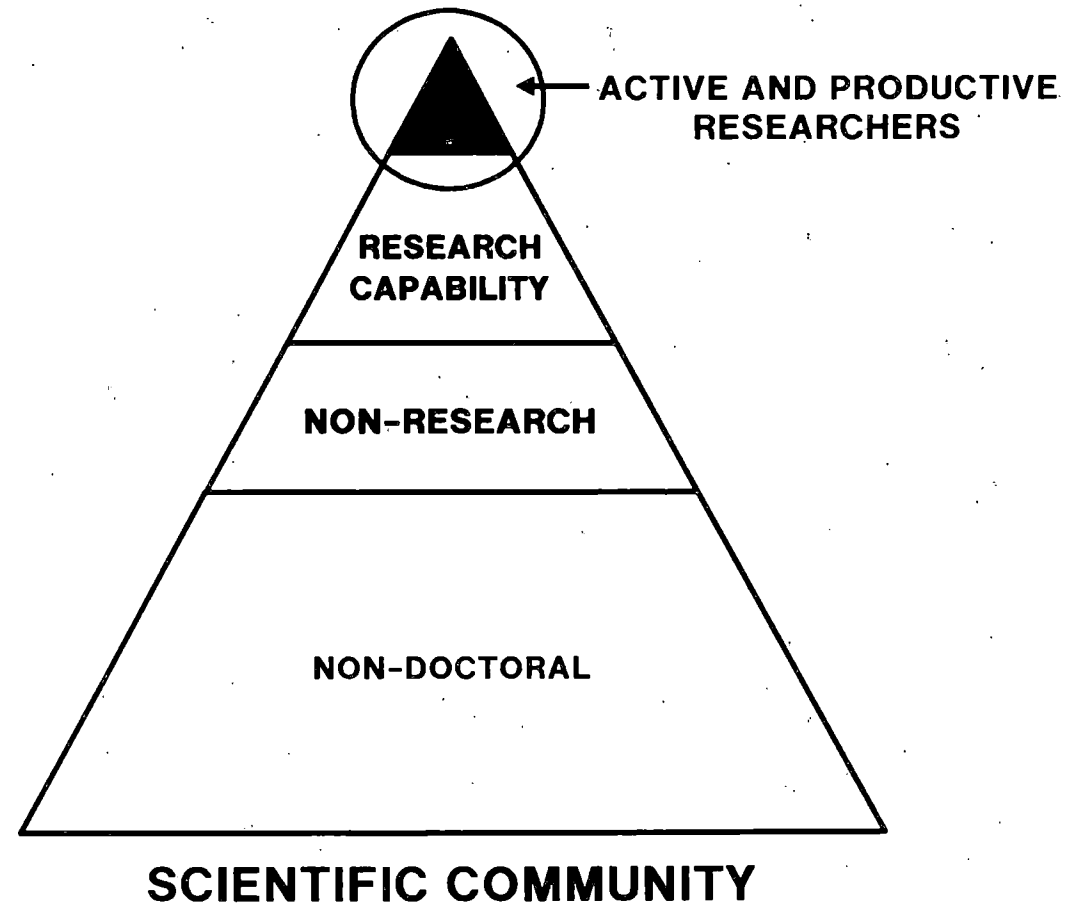
EXECUTIVE SECRETARY

- **PERFORMS ADMINISTRATIVE AND TECHNICAL REVIEW OF APPLICATIONS**
- **SELECTS REVIEWERS**
- **MANAGES STUDY SECTIONS**
- **PREPARES SUMMARY STATEMENTS**
- **PROVIDES ANY REQUESTED INFORMATION ABOUT STUDY SECTION RECOMMENDATIONS**

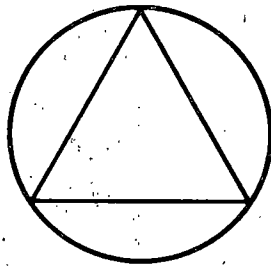
GRANTS ASSISTANT

- **MAINTAINS ORGANIZATION OF STUDY SECTION OFFICE**
- **ASSISTS EXECUTIVE SECRETARY WITH ADMINISTRATIVE AND TECHNICAL REVIEW OF APPLICATIONS**
- **MAKES PREPARATIONS FOR STUDY SECTION MEETINGS AND PROJECT SITE VISITS**
- **SHARES ADMINISTRATIVE RESPONSIBILITIES AT MEETINGS**
- **PREPARES SUMMARY STATEMENTS FOR PRINTING AND DISTRIBUTION**

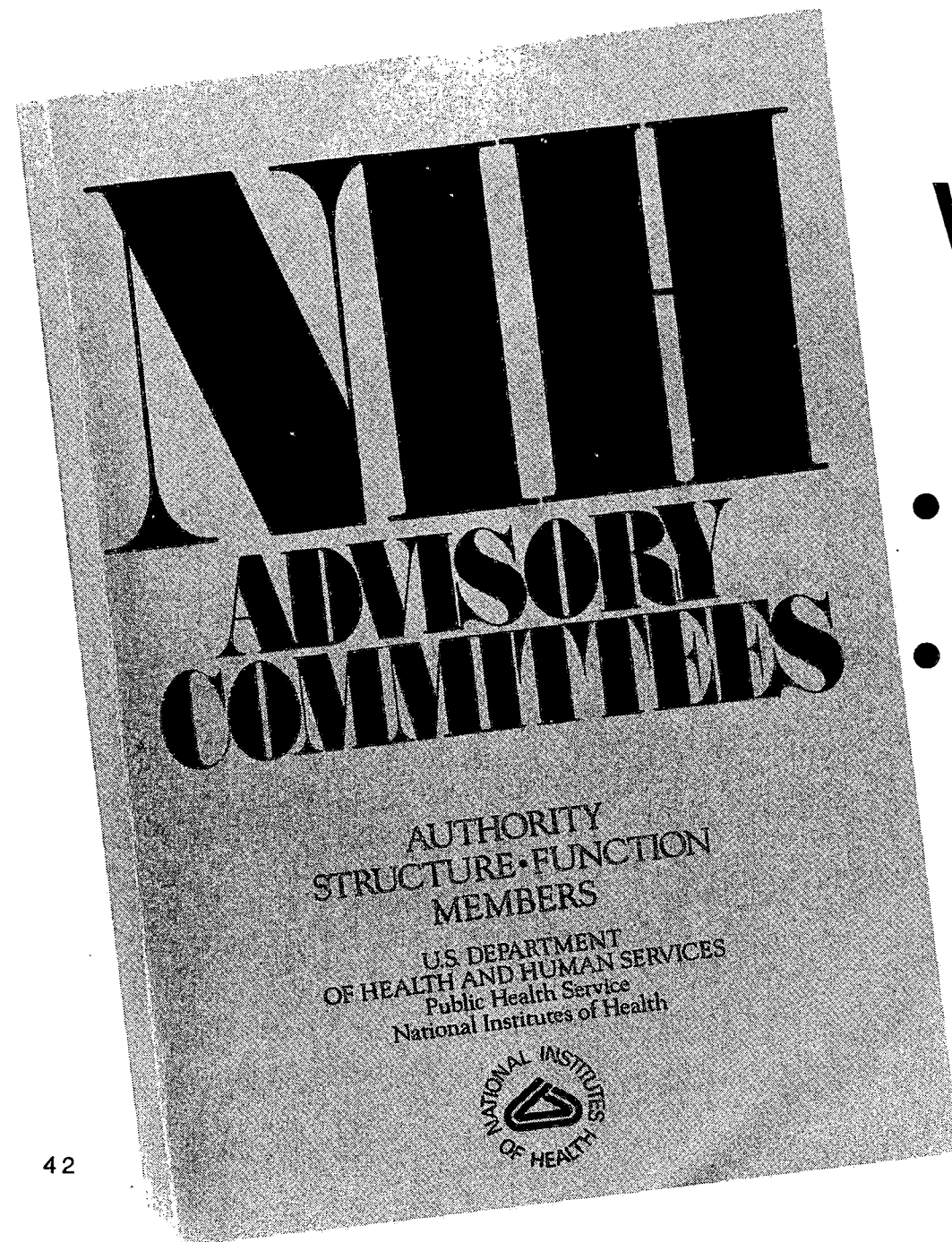
SELECTION OF PEER REVIEWERS



CRITERIA FOR SELECTION OF PEER REVIEWERS



- **DEMONSTRATED SCIENTIFIC EXPERTISE**
- **DOCTORAL DEGREE OR EQUIVALENT**
- **MATURE JUDGEMENT**
- **BALANCED PERSPECTIVE AND OBJECTIVITY**
- **ABILITY TO WORK EFFECTIVELY IN A
GROUP CONTEXT**
- **INTEREST IN SERVING**
- **ADEQUATE REPRESENTATION OF WOMEN
AND MINORITY SCIENTISTS**



WHO ARE THE REVIEWERS?

- UPDATED IN APRIL AND OCTOBER OF EACH YEAR
- AVAILABLE FROM
DIVISION OF RESEARCH
GRANTS COMMITTEE
MANAGEMENT OFFICE
NAT. INST. HEALTH
BETHESDA MD 20892

DRG STUDY SECTIONS

STUDY SECTION	CODE	STUDY SECTION	CODE
ALLERGY AND IMMUNOLOGY	(ALY)	METALLOBIOCHEMISTRY	(BMT)
BACTERIOLOGY AND MYCOLOGY	(BM)	MICROBIAL PHYSIOLOGY AND GENETICS	(MBC)
BEHAVIORAL AND NEUROSCIENCES-FELLOWSHIPS	(BNS)	MOLECULAR AND CELLULAR BIOPHYSICS	(BBCA)
BEHAVIORAL MEDICINE	(BEM)	MOLECULAR BIOLOGY	(MBY)
BIOCHEMICAL ENDOCRINOLOGY	(BCE)	MOLECULAR CYTOLOGY	(CTY)
BIOCHEMISTRY	(BIO)	NEUROLOGICAL SCIENCES	(NLS)
BIOMEDICAL SCIENCES-FELLOWSHIPS	(BI)	NEUROLOGY A	(NEUA)
BIO-ORGANIC AND NATURAL PRODUCTS CHEMISTRY	(BNP)	NEUROLOGY B	(NEUB)
BIOPHYSICAL CHEMISTRY	(BBCB)	NEUROLOGY C	(NEUC)
BIO-PSYCHOLOGY	(BPO)	NURSING RESEARCH	(NURS)
CARDIOVASCULAR AND PULMONARY	(CVA)	NUTRITION	(NTN)
CARDIOVASCULAR AND RENAL	(CVB)	ORAL BIOLOGY AND MEDICINE	(OBM)
CELLULAR BIOLOGY AND PHYSIOLOGY	(CBY)	ORTHOPEDICS AND MUSCULOSKELETAL	(ORTH)
CHEMICAL PATHOLOGY	(CPA)	PATHOBIOCHEMISTRY	(PBC)
CLINICAL SCIENCES-FELLOWSHIPS	(CLN)	PATHOLOGY A	(PTHA)
DIAGNOSTIC RADIOLOGY	(RNM)	PATHOLOGY B	(PTHB)
ENDOCRINOLOGY	(END)	PHARMACOLOGY	(PHRA)
EPIDEMIOLOGY AND DISEASE CONTROL	(EDC)	PHYSICAL BIOCHEMISTRY	(PB)
EXPERIMENTAL CARDIOVASCULAR SCIENCES	(ECS)	PHYSIOLOGICAL CHEMISTRY	(PC)
EXPERIMENTAL IMMUNOLOGY	(EI)	PHYSIOLOGY	(PHY)
EXPERIMENTAL THERAPEUTICS	(ET)	RADIATION	(RAD)
EXPERIMENTAL VIROLOGY	(EVR)	REPRODUCTIVE BIOLOGY	(REB)
GENERAL MEDICINE A	(GMA)	REPRODUCTIVE ENDOCRINOLOGY	(REN)
GENERAL MEDICINE B	(GMB)	RESPIRATORY AND APPLIED PHYSIOLOGY	(RAP)
GENETICS	(GEN)	SENSORY DISORDERS AND LANGUAGE	(CMS)
HEARING RESEARCH	(HAR)	SOCIAL SCIENCES AND POPULATION	(SSP)
HEMATOLOGY	(HEM)	SPECIAL PROGRAMS	(SSS)
HUMAN DEVELOPMENT AND AGING	(HUD)	SURGERY AND BIOENGINEERING	(SB)
HUMAN EMBRYOLOGY AND DEVELOPMENT	(HED)	SURGERY, ANESTHESIOLOGY, AND TRAUMA	(SAT)
IMMUNOBIOLOGY	(IMB)	TOXICOLOGY	(TOX)
IMMUNOLOGICAL SCIENCES	(IMS)	TROPICAL MEDICINE AND PARASITOLOGY	(TMP)
MAMMALIAN GENETICS	(MGN)	VIROLOGY	(VR)
MEDICINAL CHEMISTRY	(MCHA)	VISUAL SCIENCES A	(VISA)
METABOLIC PATHOLOGY	(MEP)	VISUAL SCIENCES B	(VISB)
METABOLISM	(MET)		

VARIED EXPERTISE ON A SAMPLE STUDY SECTION

SURGERY, ANESTHESIOLOGY AND TRAUMA STUDY SECTION
SELECTED AREAS OF COMPETENCE OF MEMBERS
BIOCHEMISTRY BURN PHYSIOLOGY AND ELECTROLYTE METABOLISM CARDIOVASCULAR AND PULMONARY PHYSIOLOGY CLINICAL ANESTHESIOLOGY DRUG METABOLISM (ANESTHETICS) GENERAL SURGERY IMMUNOLOGY AND TRANSPLANTATION NUTRITION PHARMACOLOGY (ANALGESICS, NARCOTICS AND ANTAGONISTS) PULMONARY EMBOLISM SHOCK AND TRAUMA TOXICOLOGY OF ANESTHETIC DRUGS UROLOGY VASCULAR SURGERY

RESEARCH GRANTS

REVIEW CRITERIA

- **SIGNIFICANCE AND ORIGINALITY FROM A SCIENTIFIC AND TECHNICAL STANDPOINT.**
- **ADEQUACY OF THE METHODOLOGY TO CARRY OUT THE RESEARCH.**
- **QUALIFICATIONS AND EXPERIENCE OF THE PRINCIPAL INVESTIGATOR AND STAFF.**
- **REASONABLE AVAILABILITY OF RESOURCES.**
- **REASONABLENESS OF THE PROPOSED BUDGET AND DURATION.**
- **OTHER FACTORS: HUMAN SUBJECTS, ANIMAL WELFARE, BIOHAZARDS, ETC.**

STUDY SECTION ACTIONS

- **APPROVAL**
 - **SCIENTIFIC MERIT RATING
(PRIORITY SCORE)**
- **DISAPPROVAL**
- **DEFERRAL**

ACTION

APPROVAL:

BASED ON THE RELEVANT REVIEW CRITERIA, THE APPLICATION IS OF SUFFICIENT MERIT TO BE WORTHY OF SUPPORT. THE VOTE FOR APPROVAL IS EQUIVALENT TO A RECOMMENDATION THAT AN AWARD BE MADE PROVIDED SUFFICIENT FUNDS ARE AVAILABLE. THE RECOMMENDATION CAN BE FOR THE TIME AND AMOUNT REQUESTED OR FOR AN ADJUSTED TIME AND AMOUNT. A PRIORITY SCORE IS REQUIRED.

PRIORITY SCORES

PRIORITY SCORES ARE ASSIGNED EACH APPLICATION. THE SCORES RANGE FROM 1.0 (OUTSTANDING) TO 5.0 (ACCEPTABLE.)

ACTION

DISAPPROVAL:

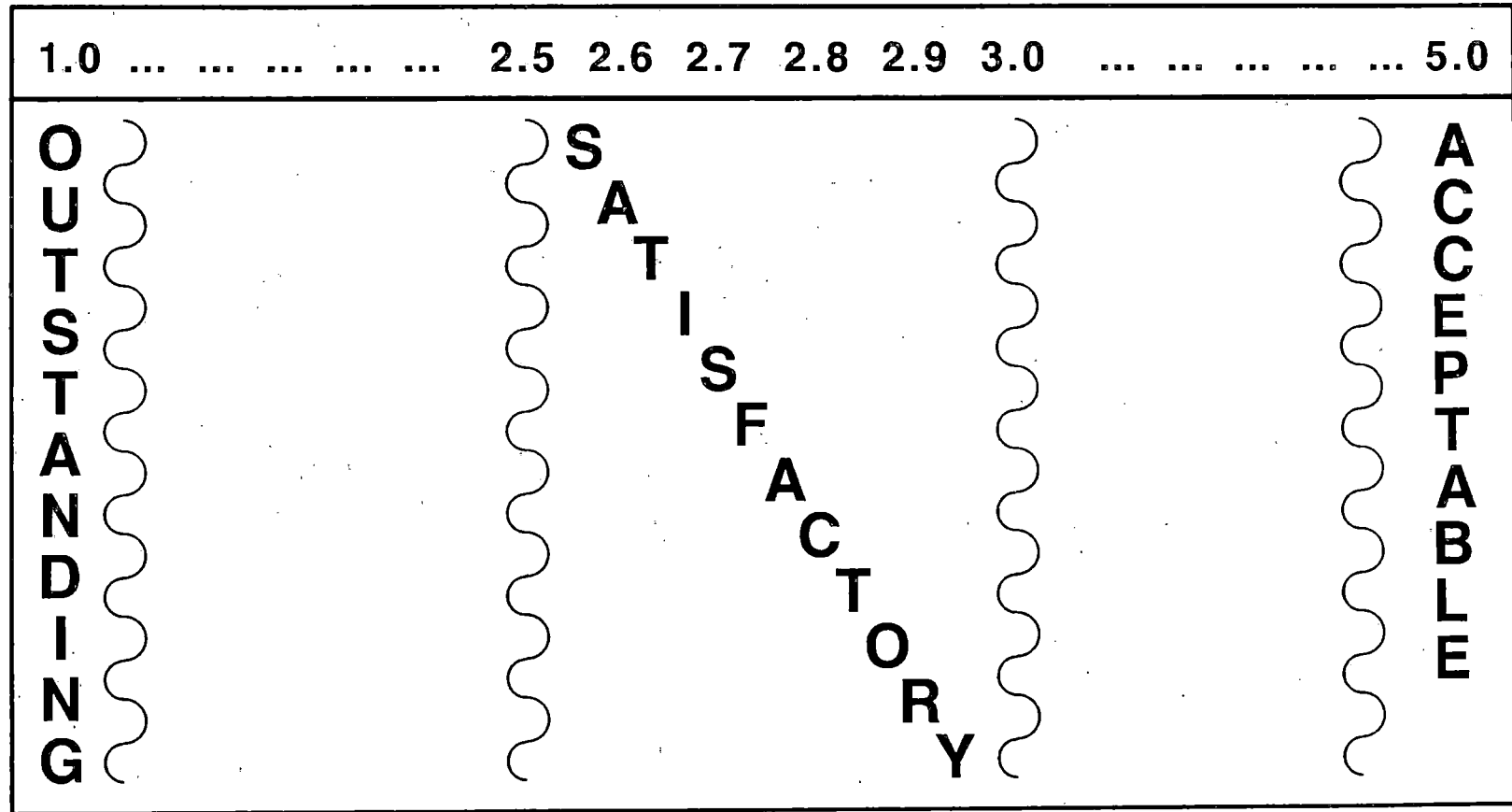
THE APPLICATION IS NOT OF SUFFICIENT MERIT TO BE WORTHY OF SUPPORT. DISAPPROVAL ALSO MAY BE RECOMMENDED WHEN GRAVELY HAZARDOUS OR UNETHICAL PROCEDURES ARE INVOLVED, OR WHEN NO FUNDS CAN BE RECOMMENDED, SUCH AS IN THE CASE OF A SUPPLEMENT DEEMED TO BE UNNECESSARY. NO PRIORITY SCORE IS REQUIRED.

ACTION

DEFERRAL:

THE STUDY SECTION CANNOT MAKE A RECOMMENDATION WITHOUT ADDITIONAL INFORMATION. THIS INFORMATION MAY BE OBTAINED BY A PROJECT SITE VISIT OR BY SUBMISSION OF ADDITIONAL MATERIAL BY THE APPLICANT.

PRIORITY SCORE



QUALITY RATING SCALE

PROJECT SITE VISITS: RESEARCH GRANTS

WHEN?

- **BEFORE STUDY SECTION MEETING**
- **AFTER STUDY SECTION DEFERRAL RECOMMENDATION**
- **AFTER COUNCIL DEFERRAL RECOMMENDATION**

WHY?

- **NEEDED INFORMATION AVAILABLE ONLY AT PROPOSED RESEARCH OR TRAINING SITE**

BY WHOM?

- **MEMBERS OF THE STUDY SECTION**
- **AD HOC CONSULTANTS AS NEEDED**
- **EXECUTIVE SECRETARY**
- **INSTITUTE PROGRAM STAFF**

CONFIDENTIALITY

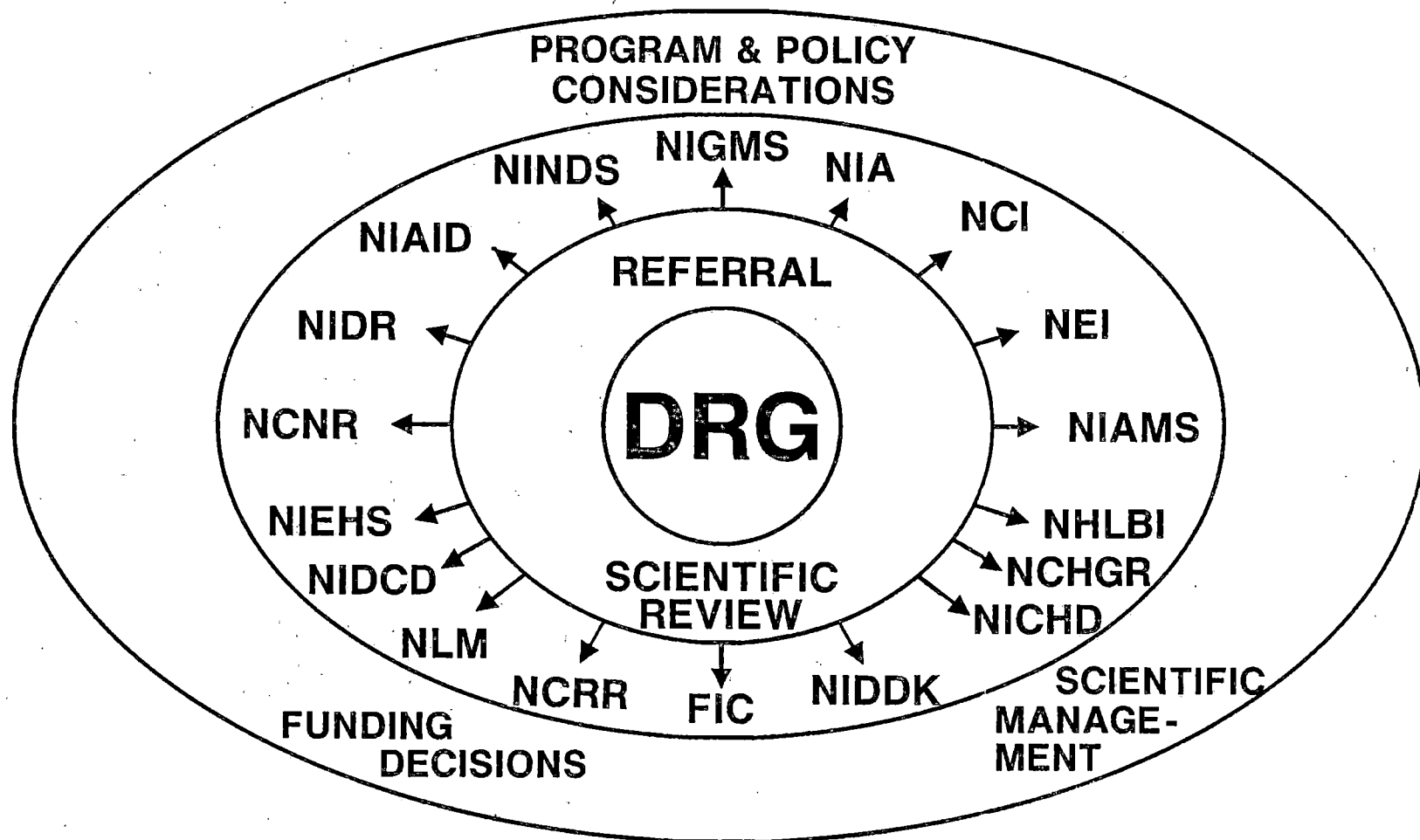
- **REVIEW MATERIALS AND PROCEEDINGS OF REVIEW MEETINGS REPRESENT PRIVILEGED INFORMATION TO BE USED ONLY BY CONSULTANTS AND NIH STAFF.**
- **AT THE CONCLUSION OF EACH MEETING, CONSULTANTS WILL BE ASKED TO LEAVE PROPOSALS AND OTHER MATERIALS SENT TO THEM.**
- **CONSULTANTS SHOULD NOT ADVISE APPLICANTS OF RECOMMENDATIONS. QUESTIONS SHOULD BE REFERRED TO NIH STAFF.**

CERTIFICATION OF NO CONFLICT OF INTEREST

THIS WILL CERTIFY THAT IN THE REVIEW OF APPLICATIONS AND PROPOSALS BY _____ ON _____, I DID NOT PARTICIPATE IN THE DISCUSSION OF ANY APPLICATION OR PROPOSAL FROM AN ORGANIZATION INSTITUTION, OR UNIVERSITY SYSTEM WHERE I AM AN EMPLOYEE, CONSULTANT, OFFICER, DIRECTOR, OR TRUSTEE, OR HAVE A FINANCIAL INTEREST. I WAS NOT INVOLVED IN THE REVIEW OF ANY APPLICATION OR PROPOSAL IN WHICH THERE WAS A REAL OR APPARENT CONFLICT OF INTEREST.

SIGNATURES

NIH REFERRAL AND REVIEW SYSTEM REGULAR RESEARCH GRANT APPLICATIONS



**NATIONAL ADVISORY COUNCIL
OR BOARD REVIEW**

COUNCIL ACTIONS

- **CONCURRENCE WITH STUDY SECTION ACTION**
- **MODIFICATION OF STUDY SECTION ACTION BASED ON PROGRAM OR POLICY CONSIDERATIONS**
- **DEFERRAL FOR FURTHER REVIEW**

WHAT DETERMINES WHICH AWARDS ARE MADE?

- **SCIENTIFIC MERIT**
- **PROGRAM CONSIDERATIONS**
- **AVAILABILITY OF FUNDS**

MOST COMMON REASONS FOR DISAPPROVAL

- **LACK OF NEW OR ORIGINAL IDEAS**
- **DIFFUSE, SUPERFICIAL, OR UNFOCUSED RESEARCH PLAN**
- **LACK OF KNOWLEDGE OF PUBLISHED RELEVANT WORK**
- **LACK OF EXPERIENCE IN THE ESSENTIAL METHODOLOGY**
- **UNCERTAINTY CONCERNING THE FUTURE DIRECTIONS**
- **QUESTIONABLE REASONING IN EXPERIMENTAL APPROACH**
- **ABSENCE OF AN ACCEPTABLE SCIENTIFIC RATIONALE**
- **UNREALISTICALLY LARGE AMOUNT OF WORK**
- **LACK OF SUFFICIENT EXPERIMENTAL DETAIL**
- **UNCRITICAL APPROACH**

RESEARCH MANPOWER

RESEARCH TRAINING AND DEVELOPMENT GRADUATE STUDENT

**MECHANISM
OF SUPPORT**

**FIRST INDEPENDENT RESEARCH SUPPORT &
TRANSITION (FIRST) AWARD (R29)**

**PREDOCTORAL TRAINING
SUPPORT (T32)**

**RESEARCH PROJECT
GRANT (R01)**

**POSTDOCTORAL
TRAINING SUPPORT
(T32,F32)**

SENIOR FELLOWSHIP (F33)

**RESEARCH CAREER
DEVELOPMENT
AWARD (K04)**

YEARS



**GRADUATE
STUDENT**

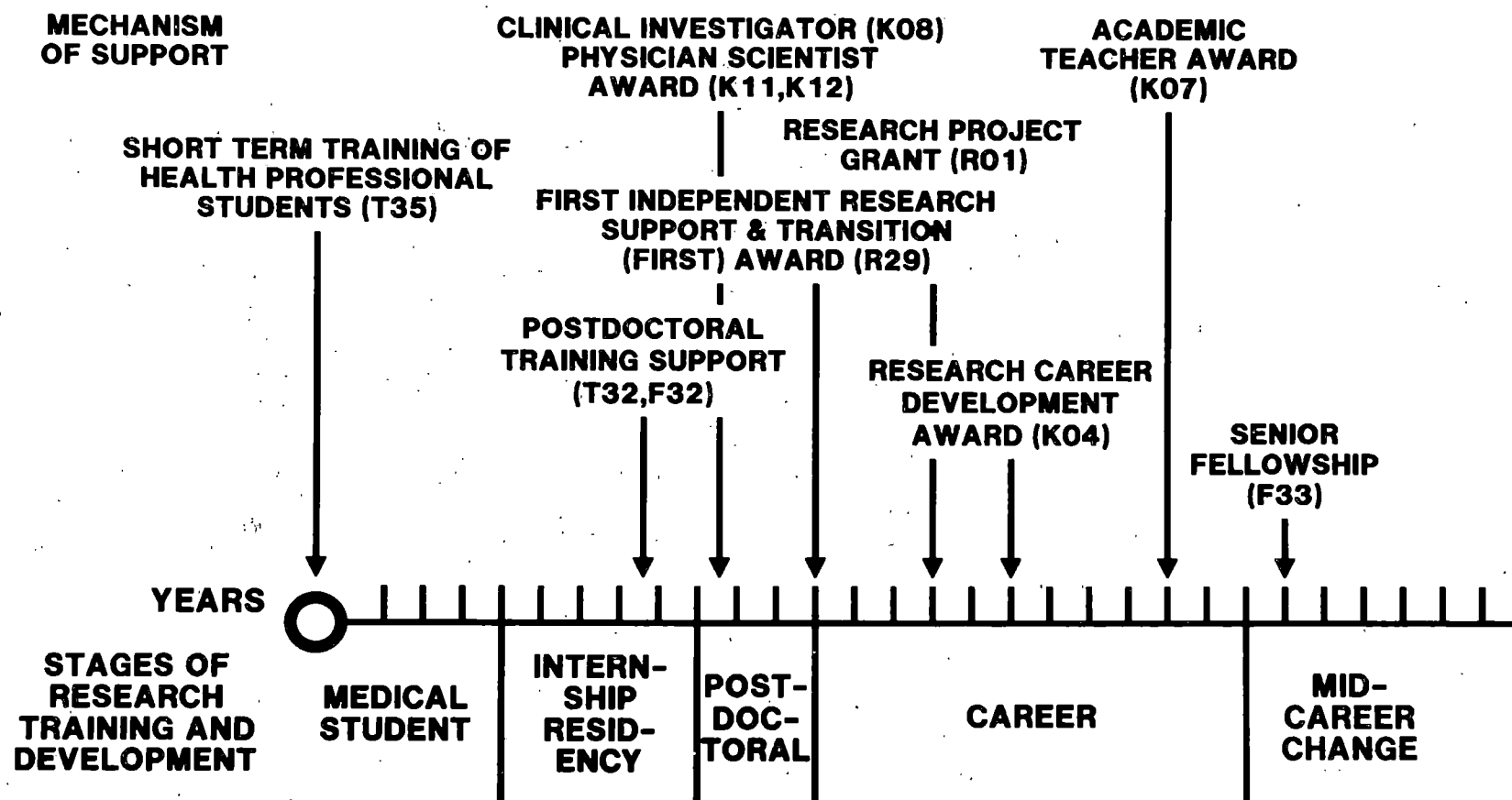
**POST-
DOCT-
ORAL**

CAREER

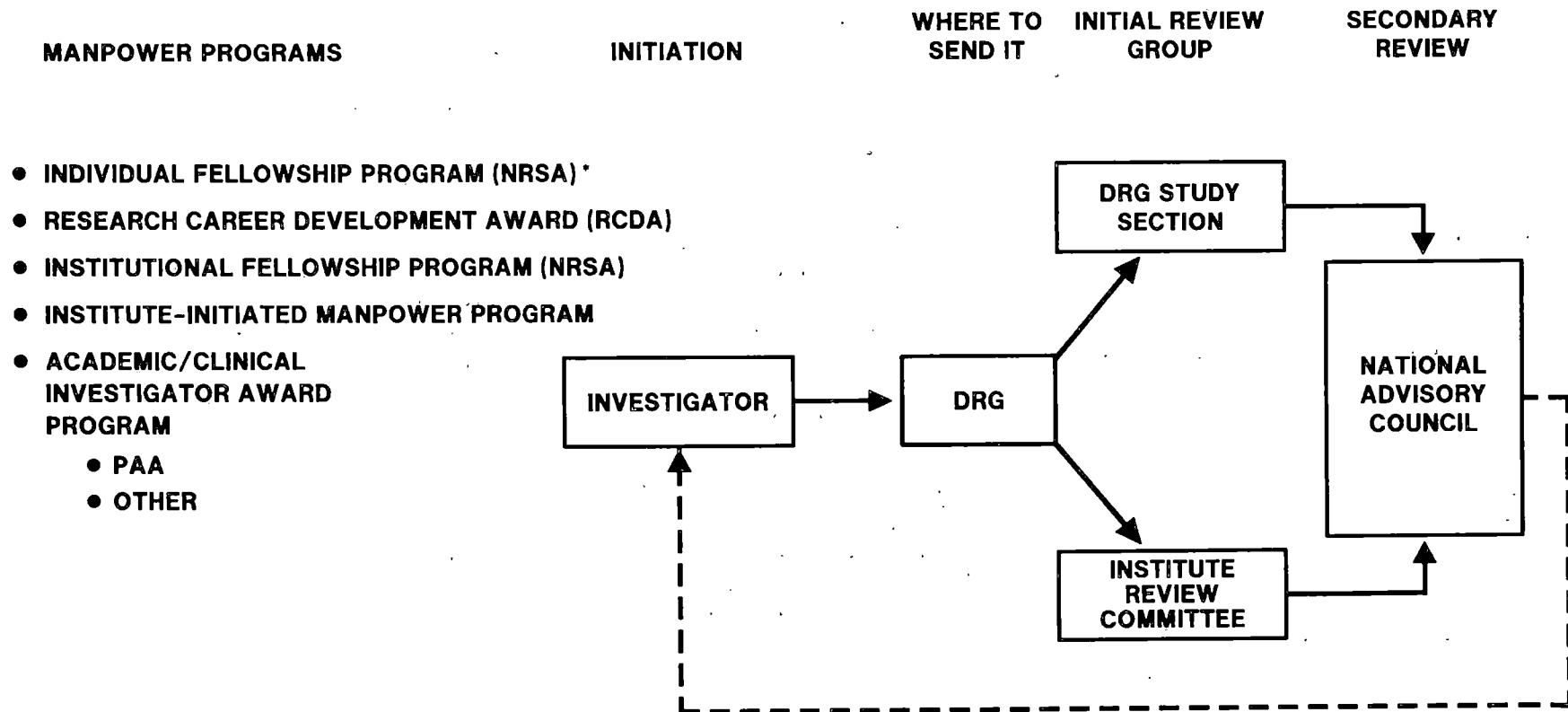
**MID-
CAREER
CHANGE**

**STAGE OF
RESEARCH
TRAINING AND
DEVELOPMENT**

RESEARCH TRAINING AND DEVELOPMENT MEDICAL STUDENT



THE IMPORTANT STEPS OF AN APPLICATION FOR RESEARCH MANPOWER PROGRAMS



*DOES NOT REQUIRE COUNCIL REVIEW

**NIH INFORMATION
SOURCES**

1. Research Grants Policy

- Dr. John W. Diggs, Deputy Director for Extramural Research, Office of the Director, NIH, (301) 496-1096
- Dr. George Galasso, Associate Director for Extramural Affairs, Office of the Director, NIH, (301) 496-5356
- Dr. James F. O'Donnell, Director, Office of Extramural Programs, Office of the Director, (301) 402-0854
- Mr. Geoffrey E. Grant, Grants Policy Officer, Office of the Director, (301) 496-5967
- Dr. William H. Goldwater, NIH Extramural Programs Management Officer, (301) 496-2241
- Dr. Samuel H. Joseloff, Chief, Office of Grants Inquiries, Division of Research Grants, (301) 496-7441

2. Research Training Policy

- Dr. Walter T. Schaffer, Research Training and Research Resources Officer, Office of the Director, (301) 496-9743

3. Receipt and Assignment of Applications (Referral Section, Referral and Review Branch, Division of Research Grants)

- Dr. Patricia Ann Straat, Deputy Chief for Referral, (301) 496-7447
- Dr. Julius Currie, Assistant Chief, (301) 496-7447
- Dr. Rosemary Morris, Assistant Chief, (301) 497-7447
- Dr. Suzanne Fisher, Assistant Chief, (301) 496-7447
- Ms. Jean Malcolm, Chief, Project Control Unit, (301) 496-7324

4. Scientific Merit Review of Applications

a. Division of Research Grants

- Dr. Jerome G. Green, Director, (301) 496-7211
- Dr. Anthony Demsey, Associate Director for Referral and Review, (301) 496-7023
- Dr. Faye Calhoun, Deputy Chief for Review, Referral and Review Branch, (301) 496-7023
- Dr. Raymond E. Babor, Associate Chief for Review, Referral and Review Branch, (301) 496-8844
- Appropriate Section Chief, Executive Secretary, or Grants Technical Assistant

b. NIH Awarding Component

- Dr. Arthur Broering (acting) , National Library of Medicine, (301) 496-4621
- Dr. Kenneth Bridbord, Fogarty International Center, (301) 496-1653
- Dr. Miriam Keltz, National Institute on Aging, (301) 496-9322
- Ms. Barbara Bynum, National Cancer Institute, (301) 496-5147
- Dr. Ronald G. Geller, National Heart, Lung, and Blood Institute, (301) 496-7416
- Mr. Donald Clark, National Institute of Child Health and Human Development, (301) 496-5001
- Dr. Lois Cohen, National Institute of Dental Research, (301) 496-6705
- Dr. John Dalton, National Institute of Neurological Disorders and Stroke, (301) 496-9248
- Dr. Luz Froehlich, National Institute of Allergy and Infectious Diseases, (301) 496-7291
- Dr. Michael D. Lockshin, National Institute of Arthritis and Musculoskeletal and Skin Diseases, (301), 496-0802
- Dr. Jack A. McLaughlin, National Eye Institute, (301) 496-4903
- Dr. Ralph F. Naunton (acting), National Institute of Deafness and Other Communication Disorders, (301) 496-1804
- Dr. Judith L. Vaitukaitis, National Center for Research Resources, (301), 496-6023
- Dr. Anne B. Sassaman, National Institute of Environmental Health Services, (919) 541-7723
- Dr. Walter Stolz, National Institute of Diabetes and Digestive and Kidney Diseases, (301) 496-7277
- Dr. Sue Shafer, National Institute of General Medical Sciences, (301) 496-7063
- Dr. Mark Guyer, National Center for Human Genome Research, (301) 496-0844
- Dr. Janet Heinrich, National Center for Nursing Research, (301) 496-0523
- Appropriate Executive Secretary, Program Staff Member, Grants Management Officer, or Grants Technical Assistant

5. General Information

a. Research Involving Human Subjects or Animals

- Dr. Charles McCarthy, Director, Office for Protection from Research Risks, (301) 496-7005
- Dr. John G. Miller, Director, Division of Animal Welfare, (301) 496-7163
- Mr. F. William Dommel, Director, Division of Human Subject Protection, (301) 496-8101

b. Privacy Act

- Ms. Barbara E. Bullman, NIH Privacy Act Officer, (301) 496-2832
- Appropriate NIH Component Privacy Act Coordinator

c. Freedom of Information Act

- Ms. Joanne Belk, NIH Freedom of Information Act Officer, (301) 496-5633
- Appropriate NIH Component Freedom of Information Act Coordinator

d. Public Information

- Mr. Storm Whaley, Associate Director for Communication, Office of the Director, (301) 496-4461
- Ms. R. Anne Thomas, Director, Division of Public Information, Office of the Director, (301) 496-5787

e. Single Copies of Publications and Application Kits (Extramural Support)

- Dr. Samuel H. Joseloff, Chief, Office of Grants Inquiries, Division of Research Grants, (301) 496-7441

REFERENCE ARTICLES

- "NIH Grant Applications for Clinical Research: Reasons for Poor Ratings or Disapproval," *Clinical Research* 31: 453-461, 1983.
- "Why Clinical Research Grant Applications Fare Poorly in Review and How to Recover," *Cancer Investigation*: 5(1), 55-58, 1987.
- "Review of Research Grant Applications at the National Institutes of Health," (Updated version (1982) of "Who reads your project-grant application to the National Institutes of Health?" *Federation Proceedings* 31: 2-9, 1972.)
- "The project-grant application of the National Institutes of Health." *Federation Proceedings* 32: 1541-1550, 1973.
- "The grant application: an exercise in scientific writing." *Federation Proceedings* 32: 1541-1543, 1973.
- "A successful grant application to the National Institutes of Health: case history." *Grants Magazine* 1: 263-283, 1978
- "Ingredients of a Successful Grant Application to the National Institutes of Health." *Journal of Orthopaedic Research* 7: 138-141, 1989.
- "Obtaining Grant Funding for Clinical Research." *Non-Cemented Total Hip Arthroplasty* 41: 473-478, 1988.
- "Site visits for the review of grant applications to the National Institutes of Health; views of an applicant and a scientist administrator." *Federation Proceedings* 34: 131-136, 1975.
- "Application and Review Procedures for the NIH Small Business Innovation Research Program," *Institute Insight*, 1-12, March 1984.
- "Biomedical Research and Research Training Support by the National Institutes of Health," *Nutrition International* 2: 38-44, 1986.
- National Institutes of Health, Report of the NIH Peer Review Committee, December 1988.