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ABSTRACT

The paper reviews mental retardation research activities of the National Institute of Child Health and Human Development (NICHD) and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). Research activities are cited to illustrate the scope of NICHD's efforts in a variety of biomedical areas. Activities are described for the following topics: malnutrition and development (effects of protein malnutrition on brain development in rats); Down Syndrome (use of mouse models to study genetic disorders); prematurity (identification of factors resulting in infant mortality, prematurity, and delayed or retarded growth and behavior development); fragile X syndrome (prenatal demonstration in cultured amniotic fluid cells); congenital hypothyroidism (effects of early treatment); phenylketonuria--PKU (assessment of the neuropsychological development of children with PKU); monitors to measure blood sugar; and psychophysiological processes (computer linked measurements of infant reactions). Activities sponsored by NINCDS center on metabolic disorders such as lipid storage diseases. (CL)

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Special Report to Congress:

MENTAL RETARDATION

FY 1983

National Institute of Child Health and Human Development

EC 17088

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

MENTAL RETARDATION

Mental retardation is a complex and many-faceted condition which ranks among the nation's most pressing social and health problems. The inadequately developed intelligence which characterizes the retarded person is present early in life and, if uncorrected, continues through maturity. Throughout its course, mental retardation impacts heavily on the individual, his or her family and community, and the economic life and resources of our nation. The complex phenomena subsumed under the term mental retardation stem from more than 200 different causes and are expressed most commonly as the product of the interaction of multiple biological, behavioral and social variables.

Different estimates have been made of the prevalence of mental retardation. The traditional method, based upon the normal distribution of intelligence test scores, provides an estimate of the number of mentally retarded Americans in excess of 6.6 million, or 3 percent of the general population. Some authorities, employing more exclusive 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 IQ's up to 80 and with problems in social adaptation.

In response to society's humanitarian concern for the mentally retarded, programs for prevention, care, treatment, education and habilitation have expanded over the past 20 years. These extensive programs involve, either directly or indirectly, most agencies of government at the Federal, state and community levels. The cost of these programs is staggering.

Under the provisions of Public Laws 94:142 and 89:313, the Department of Education reports annually on the number of handicapped children receiving special education and related services. More than 900,000 retarded children between the ages of 3 and 21 years received those services in 1980. This number represents about 1.9 percent of the total school population and more than 23 percent of the 3.9 million school age population designated as handicapped.

The costs for providing special education and related services for the educable retarded, those only mildly impaired, are estimated to be twice those for regular classroom instruction. For the trainable mentally retarded students, those with more severe impairments, costs of training are estimated to be 2.2 to 3.5 times those required for non-handicapped children. For the school age children identified as retarded in 1980, the estimated costs for their special education are about \$2 billion in 1970 dollars.

The greatest hope for a solution to the problem of mental retardation lies in its prevention and, when this is not possible, in the promotion of the individual's maximum skills through a wide-range of habilitative and restorative

procedures. Within the National Institutes of Health (NIH), these efforts are major concerns for the National Institute of Child Health and Human Development (NICHD) and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

The NICHD program of research embraces the full range of problems associated with mental retardation. Its research program relates to many of the more than 200 mental retardation syndromes and is concerned with both the preventive and ameliorative aspects of the problem. The 12 Mental Retardation Research Centers (MRRCs), funded by the NICHD and administered by the Institute's Mental Retardation and Developmental Disabilities Branch (MRDD), are major contributors to the national research effort on mental retardation. In FY 1982, the Institute supported 137 extramural research grants and contracts directly concerned with the epidemiology, etiology, diagnosis, prevention and amelioration of mental retardation. The scope of the problems attacked and progress toward their solution are indicated in the reports of research activities which follow.

Research Activities

Malnutrition and Development

NICHD is providing research grant support to Dr. Oscar Resnick at the Worcester Foundation in Shrewsbury, Massachusetts to investigate the effects of protein malnutrition on brain development using rats as an experimental model. The use of the protein malnourished animal is relevant to the problems of mental retardation because poor nutrition has a deleterious effect on brain maturation and function. Since it is impossible to isolate nutritional factors in the human from genetic, social, and cultural factors, the rat model is a useful system for the study of mental retardation. The investigators have reported that when rats are placed on a diet containing 8 percent protein five weeks prior to mating and during gestation, the litter size, the weight of the pups and the weight of the pup brains were identical to control pups whose mothers were fed on a 25 percent protein diet. Both diets contained the same amounts of calories. Even though the 8 percent rats appeared to be "normal" at birth, they displayed many brain and peripheral metabolic imbalances compared to normal animals at this age. The chemical changes were irreversible even though the body and brain weights were normal throughout life as a result of letting the protein-deprived pups nurse from well-nourished dams at birth. Therefore, the inability of adequate nutrition during lactation to restore metabolic alterations in the central nervous system which were initiated before birth indicates the seriousness of mild fetal protein insufficiencies. These insufficiencies would not be detected by either an assessment of "normal" birth weights or by optimal weight gains during the nursing period. If these data in the rat can be extrapolated to humans, it is possible that similar forms of mild protein deficiency during pregnancy occur in women and are overlooked because the birth weight of the child is within the "normal" range.

When these experiments were repeated using a diet containing 6 percent protein, the litter size was decreased and the weight of the pups and their brains were decreased. When the 6 percent pups were allowed at birth to nurse

from dams on a normal (25 percent) protein diet, their body weights did not recover fully. In addition, the same chemical effects on the brain and periphery were noticed, only they were of a larger magnitude. As with the 8 percent pups, the central and peripheral chemical changes could not be reversed by nursing from well-nourished dams at birth.

Down Syndrome

Down syndrome is the most common and readily identifiable genetic cause of mental retardation. Based on six surveys of newborns conducted between 1969 and 1975, the incidence of Down syndrome was found to be one per 800 live births. More recent evidence suggests that its incidence is decreasing to about one per 1,000 live births. The reduction in its frequency is attributed in part to public education efforts alerting women over the age of 35 to their increased risk of bearing babies with Down syndrome.

NICHD is supporting a research contract with Dr. Charles J. Epstein at the University of California at San Francisco, to develop mouse models for genetic disorders with particular emphasis on Down syndrome. The use of mouse models to study genetic diseases is based on the assumption that, although the clinical manifestations may not be the same, the mechanisms for the production of abnormalities probably are. The development of such an animal model would allow many studies which would be difficult to carry out in man. Such studies include detailed analysis of the development of abnormalities; investigations of excised and living cells, tissues, and particularly the central nervous system; studies of pre- and post-implantation stages; gene dosage studies; and effects of genetic and environmental factors on the development of cytogenetic abnormalities.

The investigators, with the demonstration of a new gene, have added to the number of genes which are known to be on human chromosome 21 (the chromosome involved in Down syndrome) are on mouse chromosome 16. Three such genes have been demonstrated. These findings greatly strengthen the evidence for homologous (structurally similar) regions on the two chromosomes. The investigators have also produced a number of leads to further similar clinical effects of the (mouse) trisomy 16 and (human) trisomy 21. These include congenital heart disease, slower growth rate, and defects in eyelid development.

Prematurity: Causes, Effects, Prevention

The prematurity rate, or the number of babies born weighing 2,500 grams or less, is 6.7 percent among Hispanics, 5.8 percent among white non-Hispanics, and 12.8 percent among black non-Hispanic babies. Since the mortality rate and the incidence of mental retardation and developmental disabilities rise with decreasing birth weight, prevention of prematurity must be an important part of the research effort.

A research grant awarded to Dr. Gene P. Sackett at the University of Washington in Seattle has enabled a group of behavioral and biomedical scientists at its Child Development and Mental Retardation Center to identify factors which result in infant mortality, prematurity, and delayed or retarded growth and behavior development. The ultimate goal of the project is to prevent adverse pregnancy outcomes and developmental abnormalities in the offspring.

One component of the study uses a technique for culturing rat embryos. The technique was developed by a collaborating scientist at the University of Connecticut in Storrs to study agents in blood serum samples from female monkeys with histories of infrequent or frequent fetal mortality. All blood serum samples obtained from monkeys bred at the Primate Field Station at Medical Lake, Washington were coded and shipped to Storrs, Connecticut. Reproductive histories of the donors were not disclosed until the embryo culture test was completed and evaluation of the embryo responses were made. The blood serum classifications (whether obtained from high-risk or low-risk breeders) coincided with the reproductive histories of the donors in the majority of samples examined. This project provides an opportunity to search for a possible relation between reproductive history and the harmful effects of certain blood serum components on the developing fetus. These observations would be expected if such factors as endocrine dysfunction, immunological incompatibility, nutritional deficiencies, and chronic infectious agents--which are implicated in human fetal death--caused comparable problems in monkeys.

Fragile X Syndrome

The Fragile X syndrome is named after an apparent instability of one portion of the X chromosome. Its prevalence is estimated to be in the range of 4-5 per 10,000 males, which makes it second only to Down syndrome in frequency of an association between chromosomal abnormality and mental retardation. Males with the Fragile X syndrome manifest a number of subtle clinical features such as slightly increased head circumference, prominent forehead and jaw, enlarged ears, and enlarged testes. In addition, affected males are frequently mentally retarded, manifest speech and hearing deficiencies, impaired fine motor control, and hyperactivity. Female carriers of the marker X chromosome have a high incidence of mild mental retardation and several clinical characteristics found in affected males.

Investigators at the Rose F. Kennedy Center, Albert Einstein College of Medicine, New York, led by Dr. Harold Nitowsky in collaboration with scientists at the New York State Institute for Basic Research in Developmental Disabilities, have succeeded in the first prenatal demonstration of the fragile X chromosome in cultured amniotic fluid cells. This new development provides a reliable basis for prenatal diagnosis and genetic counseling of a potentially preventable form of mental retardation.

Congenital Hypothyroidism

The incidence of congenital hypothyroidism (characterized by a lack of or an underactive thyroid gland) is approximately 1 in 4,500 newborns. The condition is associated with mental retardation and other neuropsychological problems such as hyperactivity, short attention span, impaired spatial orientation, difficulties in fine motor coordination, and learning disabilities. Grantee, Dr. Robert Klein at Tufts University School of Medicine in Boston is studying the intellectual development of children with congenital hypothyroidism identified by newborn screening programs who were treated early. Seventy-seven children with infantile hypothyroidism were diagnosed out of 336,000 newborn infants who were screened in five New England states between January 1, 1976 and June 30, 1978. In addition, four children were diagnosed clinically on the day of birth. Thus, the probability of having the condition diagnosed

clinically in the newborn period is only about 5 percent. Conversely, 95 percent of the infants afflicted with the disorder would have been missed if it were not for the newborn screening program.

The mean IQ determined by the revised Stanford-Binet instrument at four years in 23 children, and at three years in 44 others, was 104 ± 19 . When the four children who were diagnosed clinically at birth were excluded, the mean score for the remaining 63 children was 106 ± 16 . The mean Stanford-Binet score for the 57 children in the contrast group, composed of 18 normal siblings and 39 children with normally functioning thyroid glands, was 106 ± 15 .

These data indicate that children with congenital hypothyroidism treated adequately before clinically diagnostic signs and symptoms appear are protected against neuropsychological impairment seen in hypothyroid infants treated only after a clinical diagnosis has been made. The normal mean and distribution of IQ's in treated patients suggest that mental retardation seen in untreated patients is a result of thyroid deficiency and not a concomitant of the disorder.

Phenylketonuria (PKU)

Phenylketonuria is an inborn error of metabolism in which the affected person is unable to metabolize phenylalanine, an amino acid which is essential for normal growth and development. It is associated with severe mental retardation, behavioral problems, epilepsy, and other signs of neurological impairment. With an incidence of 1 per 14,000 births, PKU is one of the most common metabolic disorders which, when untreated, invariably requires life-long institutional care. A collaborative study of 140 PKU children treated with a phenylalanine-restricted diet is being conducted in 15 medical centers across the United States. Research grant support has been awarded to Dr. Richard Koch at the Children's Hospital of Los Angeles to study the effect of diet discontinuation on the development of PKU children who had been on a phenylalanine-restricted diet since infancy. At age six years, with parental consent, each child was randomly assigned to one of two groups, either to continue on the diet, or to discontinue and be free to eat a normal diet. IQ data from children who have now reached ten years of age has now become available to permit outcome evaluations at both six years and ten years. Of the 78 children who have been followed to the ten year level, 25 who remained on a phenylalanine-restricted diet had an adjusted mean IQ of 102.6 at age ten in contrast to a mean IQ of 97.6 for 53 children who discontinued the diet. These represent a 2.4 increase in IQ for continuers and no change in IQ for discontinuers compared to their IQ scores at the age of six.

This on-going project will continue to assess the neuropsychological development of these children. Their school performance is being monitored closely and their intellectual and behavioral development is being evaluated for subtle signs of impairment.

Development of a Monitor to Measure Blood Sugar

It has been reported that newborn infants with low levels of blood sugar (hypoglycemia) are at risk for mental retardation, often due to irreversible brain damage. Hypoglycemia can exist in newborns who have no clinical signs or symptoms of this condition until brain damage has occurred. A simple, accurate,

rapid method to measure levels of blood sugar in the blood could make a significant impact in the prevention of mental retardation in the newborn nursery. Grantee, Dr. Ieland Clark at Children's Hospital Research Foundation, Cincinnati, using the principle he pioneered in the development of a device which measures oxygen levels by applying an electrode on the skin, is well on the way to developing a similar probe for glucose measurement. A by product of this effort is a small implantable glucose sensor that can be used eventually to drive an insulin metering device. This will provide a mechanism for continuous monitoring of blood glucose in patients with diabetes. Such a device may contribute to the reduction of the incidence of handicapped infants born to diabetic mothers by improved glucose control of pregnant diabetics.

Psychophysiological Processes

Infants weighing less than 1500 grams at birth are at particularly high risk for aberrant sensory, motor and cognitive development. Detecting such disorders at birth is of considerable clinical importance by identifying infants for intensive follow-up and appropriate developmental management. Dr. Diane Kurtzberg and associates from the Mental Retardation Research Center at Albert Einstein College of Medicine, Bronx, N.Y., developed an electrophysiological method which provides a sensitive index of sensory and cerebral dysfunction that can be applied to a high risk population for neonatal screening.

Computer-linked measurements of infants' reactions to visual and auditory stimuli were used to detect disorders of sensory processing and brain dysfunction in a group of very low birthweight infants. The validity of the deviant electrical activity in the brain was determined by repeated electrophysiological and behavioral testing during the first year of life. Infants with normal electrophysiological responses continued to exhibit normal developmental measures, whereas approximately half of the infants identified as neonatally deviant in either visual or auditory responses became normal electrophysiologically during the first year.

Research Training

In FY 1982, training for research careers in mental retardation was provided for 58 predoctoral and 37 postdoctoral students through 12 institutional training grant awards supported by the Institute. Support was also provided for two individual fellowship awards and one research career award.

National Institute of Neurological and Communicative Disorders and Stroke

Mental retardation research supported by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is primarily concerned with disorders of early childhood. These disorders include metabolic diseases such as Tay Sachs' and phenylketonuria (PKU); cerebral palsy; birth injuries; and spina bifida.

Scientists funded by NINCDS also conduct a variety of basic biological, biochemical, and molecular studies on the development and function of the nervous system. These studies are designed to provide new understanding of how the nervous system develops and functions, from which may emerge effective ways to prevent, cure, and treat mental retardation.

Metabolic Disorders. Lipid storage diseases are hereditary conditions in which large quantities of fatty materials (lipids) accumulate in body tissues when a particular enzyme is deficient. Many of these diseases cause mental retardation in infants. Intramural scientist, Dr. Roscoe O. Brady and associates, have perfected a technique which enables scientists to tell whether a patient has the type of Gaucher's disease which causes brain damage resulting in mental retardation. Using tissue samples from Gaucher's patients, the scientists have separated genetic variations of the abnormal enzyme. Then, with the help of a radioactive antibody, they identified the different forms of the enzyme and determined which form corresponds to each of the three types of Gaucher's disease.

NINCDS also supports a worldwide extramural research program on lipid storage diseases. Dr. Shimon Gatt, a grantee at the Hebrew University of Jerusalem, is examining the molecular basis of Gaucher's disease and the factors which interfere with normal enzyme production. Dr. Robert D. Jolly, a grantee at Massey University in New Zealand, is trying to establish a dog model for Gaucher's disease in the hope of learning more about the abnormal enzyme responsible for the disease.

In the United States, NINCDS grantee Dr. Hayata Kihara, at the University of California, Los Angeles, is attempting to purify the enzyme used in replacement therapy in patients with the lipid storage disease, metachromatic leukodystrophy. Dr. Satish K. Srivastava, a grantee at the University of Texas in Galveston, is conducting biochemical studies of a lipid storage disease called Batten-Spielmeyer-Vogt (BSV) syndrome, which causes mental retardation in children. It is hoped that this research will lead to improved diagnosis of the disorder.

NINCDS grantee Dr. Vivian E. Shih, Massachusetts General Hospital, is examining the molecular structure of the enzymes which are deficient in two amino acid disorders: PKU and hyperornithinemia. Dr. Shih is also developing procedures for

placental abnormalities are predictive of long-term neurologic, sensory, and cognitive deficits in children. The investigators are correlating a list of placental abnormalities with results from tests which measured the mental and motor development of children followed in the Project.

Also using National Collaborative Perinatal Project data, NINCDS's Dr. Sarah H. Broman and associates have identified factors which can cause or are associated with mental retardation. These include pregnancy complications such as maternal seizures and urinary tract infection, neonatal complications resulting from hypoxia (oxygen deficiency) or seizures, and low socioeconomic status of the family.

**MENTAL RETARDATION
Obligations**

	<u>1980</u>	<u>1981</u>	<u>1982</u>	<u>1983 Estimate</u>	<u>1984 Estimate</u>
Public Health Service:					
<u>National Institutes of Health:</u>					
National Institute of Child Health and Human Development.....	\$30,303,000	\$29,497,000	\$29,262,000	\$32,650,000	\$32,313,000
National Institute of Neurological & Communicative Disorders and Stroke.....	<u>10,827,000</u>	<u>10,116,000</u>	<u>8,963,000</u>	<u>9,930,000</u>	<u>10,300,000</u>
TOTAL, NIH.....	41,130,000	39,613,000	38,225,000	42,580,000	42,613,000
<u>Centers for Disease Control:</u>					
Immunization Program... Lead-Based Paint Poisoning Prevention Program.....	<u>30,363,000</u>	<u>30,713,000</u>	<u>34,715,000</u>	<u>39,260,000</u>	<u>41,889,000</u>
.....	<u>11,790,000</u>	<u>10,723,000</u>	<u>533,000</u>	<u>533,000</u>	<u>---</u>
TOTAL, CDC.....	42,153,000	41,436,000	35,248,000	39,793,000	41,889,000
<u>Health Resources and Services Administration:</u>	<u>20,800,000</u>	<u>20,400,000</u>	<u>1/</u>	<u>1/</u>	<u>1/</u>
TOTAL, PHS.....	104,083,000	101,499,000	73,473,000	82,373,000	84,502,000
<u>Social Security Administration:</u>					
Estimated payments, benefits from RSI-DI trust funds.....	916,000,000	1,105,000,000	1,130,000,000	1,175,000,000	1,245,000,000
Estimated general fund payments for supplemental security income.....	<u>784,000,000</u>	<u>887,000,000</u>	<u>993,000,000</u>	<u>1,127,000,000</u> ^{2/}	<u>980,000,000</u> ^{2/}
TOTAL SSA.....	1,700,000,000	1,992,000,000	2,123,000,000	2,302,000,000	2,225,000,000
<u>Health Care Financing Administration:</u>	<u>1,053,000,000</u>	<u>1,742,000,000</u>	<u>1,934,000,000</u>	<u>2,170,000,000</u>	<u>2,387,000,000</u>
TOTAL DHHS.....	2,857,083,000	3,835,499,000	4,130,473,000	4,554,373,000	4,696,502,000

1/ Funds included in the consolidated Maternal and Child Health Services Block Grant.

2/ Due to the timing of check issuance, increase in 1983 and decrease in 1984 reflects that checks were issued for 13 months in 1983 while checks were issued for 11 months in 1984.