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ABSTRACT

Collected in this document are reports of the National Institutes of Health's 1989 accomplishments in research on the problem of infant mortality. Reports are provided by the: (1) National Institute of Child Health and Human Development; (2) National Cancer Institute; (3) National Heart, Lung, and Blood Institute; (4) National Institute of Neurological Disorders and Stroke; (5) National Institute of Allergy and Infectious Diseases; (6) National Institute of Environmental Health Sciences; (7) National Institute of Arthritis and Musculoskeletal and Skin Diseases; (8) Division of Research Resources; and (9) National Center for Nursing Research. It is concluded that even though it is disappointing that the nation did not reach the goal for the reduction of infant mortality set at the beginning of the 1980s, there was significant progress toward the goal. The United States had an all-time low infant mortality rate in 1988, and remarkable progress was made during the 1980s in the ability to save the lives of premature and sick newborns. Research directed at reducing infant mortality has intensified in recent years. This research has led to advances in medicine and patient care, and has yielded powerful new technological tools with which to combat the problem. Application of these advances and use of the new tools will ensure that much progress will be made in the coming decade. (RH)

National Institutes of Health

Infant Mortality

1989 Research Accomplishments

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

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NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

INFANT MORTALITY

In the next decade, more than 400,000 U.S. children will die before their first birthday. Many are born too small or too soon to survive, while others die within the first year because of birth defects or sudden infant death syndrome (SIDS).

The infant mortality rate, which is the number of deaths of children under one year of age per 1,000 live births in a given year, dropped dramatically in the United States from 21.8 in 1968 to 10.1 per 1000 live births in 1987. However, the decline in the U.S. mortality rate leveled off in the early 1980s and has improved only from 10.4 per 1,000 in 1986 to 9.9 in 1987.

A comparison of the latest U.S. infant mortality rate to 17 other nations reveals that more than a dozen countries continue to have lower infant mortality rates than ours. Among those nations with lower provisional rates in 1988 were Hong Kong and Singapore, with 7.4 and 7.0 deaths per 1,000 live births respectively, Sweden with 5.58, and Japan with 4.8 deaths per 1,000. Although many sources think that the absence of a uniform international reporting system may contribute to the poor U.S. ranking, the inability to eliminate infant mortality is paradoxical for a nation that spends billions of dollars each year on scientific research and medical care and whose hospitals and neonatal intensive care units rank among the best in the world. Advances in medical technology have succeeded in saving increasing numbers of undersized, critically-ill newborns and have played a role in containing the nation's infant mortality rate. However, it is clear that the large number of low birth weight infants born in the U.S. is a major contributor to our high infant mortality rate. Infants who weigh less than 5 pounds 8 ounces (low birth weight) account for approximately 7 percent of all U.S. births but represent 60 percent of deaths occurring during the first year of life. Approximately 45 percent of the low-birth-weight deaths are associated with congenital anomalies.

Because they represent such a large proportion of the infant morality rate, any change in the incidence or survival rate of low birth weight infants will influence the infant mortality rate. The incidence of low birth weight actually increased from 6.8 percent in 1986 to 6.9 percent in 1987, which represents the highest level of low birth weight observed since 1979 when it was also 6.9 percent. This represents a worrisome deviation from recent trends: between 1970 and 1981 the low-birth-weight rate declined 1.3 percent per year and then remained fairly constant from 1981 until 1986.

There appears to be no single reason for the disproportionally high number of low-birth-weight babies born in the United States. Risk factors identified include younger and older maternal age; high parity; a poor reproductive history, especially a history of low birth weight spanning generations; low level of socioeconomic status and education; poor or no prenatal care; and smoking and substance abuse.

In many instances, pregnant women in high-risk groups--particularly poor, urban, black women--fail to get early, comprehensive prenatal care that includes screening for such potentially harmful conditions as nutritional deficiencies, smoking, alcohol or drug abuse. Early intervention to improve nutrition and reverse such social habits can reduce the chances of a low-birth-weight baby.

However, all low-birth-weight infants are not the product of high-risk pregnancies. Healthy women with good nutrition and prenatal care and no harmful social habits also deliver early because of premature labor or deliver infants who are undersized because of interuterine growth retardation. Researchers are investigating the basic biological reasons for low birth weight in such babies, as well as the explanation for such major causes of infant mortality as infectious diseases, birth defects, and SIDS.

The National Institute of Child Health and Human Development (NICHD) is the leader in the infant mortality research effort for the National Institutes of Health (NIH). Other NIH institutes that conduct or support studies related to infant mortality include the National Heart, Lung and Blood Institute (NHLBI); the National Institute of Neurological Disorders and Stroke (NINDS); the National Institute of Allergy and Infectious Diseases (NIAID); the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); the Division of Research Resources (DRR); and the National Center for Nursing Research (NCNR).

Since its inception in 1962, NICHD has sponsored studies that have helped the medical community improve the survival rates for all infants. Research efforts accelerated in 1985 with the Institute's Infant Mortality/Low Birth Weight Initiative, which encompasses many studies. The goal of each of these studies is to gain knowledge relating to the causes and prevention of infant mortality.

NICHD epidemiologists, statisticians and demographers are conducting and monitoring numerous studies designed to explore the infant mortality problem. One of their major research thrusts has been to make accurate comparisons of infant death rates among different countries, including Australia, European countries and Japan. As part of this effort, an NICHD statistical team headed by Howard J. Hoffman found significant differences among five racial and national groups examined. In comparing infant mortality rates attributable to intrauterine

growth retardation (IUGR) in U.S. blacks, U.S. whites, Aborigines, Australian whites, and Japanese, the team concluded that individual growth standards must be developed for each group.

Another multinational study explored the birth weight-specific trends in perinatal and infant mortality from 1972 to 1985. This study suggested that differences in the incidence of multiple births may contribute to the high U.S. infant mortality rate. The incidence of multiple births ranged from a low of 1.25 percent of births in Japan to about 2 percent of births in Norway, Scotland, Sweden, and among U.S. whites, to almost 2.5 percent of births to U.S. blacks. Multiple births account for a relatively higher percent of perinatal or infant deaths in all countries. Sweden has the fewest (5 percent) and the U.S. and Scotland the highest (10 to 11 percent) of deaths among multiple births.

A number of studies hope to define the contribution of lifestyles and ethnic differences to infant mortality. Lifestyles of U.S. white, black, Mexican, Chinese and Puerto Rican women will be compared to try to determine why Mexican-American infants are significantly bigger than black infants (and therefore have a better chance of survival), despite the fact that women in both ethnic groups share known risk factors associated with low income, limited education, and inadequate nutrition and prenatal care. Because black women in the U.S. have twice the risk of delivering a low-birth-weight infant as white or Hispanic women with comparable backgrounds, in addition to the known risk factors associated with low birth weight, another study will look at such factors as social support, level of physical activity, stress, and attitudes and beliefs about pregnancy. The NICHD-supported study is headed by Dr. Patricia Shiono and is conducted in prenatal clinics affiliated with Columbia University in New York City and Northwestern University in Chicago, Illinois.

Low Birth Weight

As noted above, low-birth-weight infants account for a large proportion of newborn deaths and the number of these low-birth-weight infants is increasing. Accordingly, NICHD supports more than 100 research projects on high-risk pregnancy, with the goal of increasing our understanding of why some babies are born prematurely and what factors initiate labor. Researchers are investigating the causes of premature birth and intrauterine growth retardation, both of which result in low birth weight. Through the studies, scientists hope to learn not only how they can improve the survival chances of low-birth-weight babies through further neonatal intensive care advances, but also how they can prevent low birth weight.

Improvements in Survival

The development of sophisticated, life-saving equipment in neonatal intensive care units in hospitals throughout the United States is largely responsible for the decline in newborn deaths and the infant mortality rate. Since 1960, advancing technology has dramatically reduced the number of deaths during the first 28 days of life. For babies with very low birth weight--infants who weight less than 3 pounds, 5 ounces at birth--survival rates improved from 28 percent in 1960 to 73 percent in the early 1980s. The latest data from the NICHD Neonatal Intensive Care Unit Research Network reveal that 90 percent of infants born at weights between 2 pounds 3 ounces and 3 pounds 5 ounces survive; however, only 33 percent of infants born weighing less than 1 pound 10 ounces survive. The NICHD has funded many of the life-saving technological advances that have been developed for newborns over the past 25 years. The research has led to better intravenous nutrient regimens and improved treatments for such life-threatening conditions as respiratory distress syndrome and intracranial hemorrhage, as well as various infections.

Neonatal Intensive Care Network

In 1985, NICHD formed a research network of Neonatal Intensive Care Units (NICUs) in seven university hospitals across the country. The centers, which perform large clinical trials, provide NICHD with a faster, more effective system of evaluating neonatal intensive care treatments. The NICU network is collaborating on several ongoing studies, including studies designed to document the morbidity, mortality, and requirements for care for infants with a birth weight less than 3 pounds 5 ounces. Other studies include a clinical trial to determine the effectiveness of intravenous immunoglobulin in the prevention of infection in low-birth-weight infants. More than 2,500 infants weighing less than 3 pounds, 5 ounces are included in this multi-year research project whose results will be reported next year.

The use of surfactant therapy in the prevention and treatment of respiratory distress syndrome is also under study in the NICU Network. Neonatal respiratory distress syndrome (RDS) affects 40,000 infants born in the United States each year and results in the deaths of 5,000. It is caused by the inability of the lungs of premature infants to make surfactant, a material that helps the lungs inflate easily and prevents their collapse during expiration. Surfactant is produced in the lungs of a fetus in the last trimester. Previous small studies using a variety of different surfactants and treatment regimens have documented that surfactant therapy can reduce the severity of respiratory distress syndrome and lead to a decrease in both mortality and morbidity of premature infants. In anticipation of the introduction of surfactant into routine care, the NICU network is currently studying the effectiveness of surfactant therapy to determine whether it is associated with a decrease in

the mortality rate and length of time of infants weighing 1 pound 5 ounces to 2 pounds 14 ounces at birth must spend linked to mechanical ventilation. Two surfactant preparations will be available before the end of the year under FDA-approved treatment regimens. The NICU Network will perform a large, multi-center, randomized, blinded clinical trial of the two surfactants in 1990.

Maternal-Fetal Medicine Research Network

A network of Maternal-Fetal Medicine Units (MFMUs) was also funded in 1985 to perform clinical trials designed to evaluate maternal-fetal treatments. The MFMU network is conducting a clinical trial to determine whether low-dose aspirin can prevent preeclampsia (pregnancy-induced hypertension) in women pregnant with their first child. The first 600 of the 3,000 women to be studied were enrolled in 1989. Safety studies will be conducted throughout the trial to ensure that there are no adverse effects on either the mother or the unborn child. Ancillary studies will look for biomarkers that can help scientists identify which women are likely to develop preeclampsia.

The MFMU network is also conducting a clinical trial to determine if antibiotics can enhance the effect of tocolytic medications used to arrest preterm labor. Women are taking low doses of standard antibiotics during pregnancy to determine their value in preventing preterm labor. An ancillary study will attempt to prove that infection is present by testing amniotic fluids. One hypothesis is that the body's reaction to bacteria in the amniotic fluid alters the production of enzymes that trigger preterm labor. This 24-month study of 700 pregnant women began in December 1989.

The Use of Drugs in the NICU

NICHD is also sponsoring research on medication use and adverse reactions in NICUs. Dr. Allen A. Mitchell at Boston University in Massachusetts heads a team of researchers studying the use of morphine sulfate as a sedative during medical and surgical procedures. Morphine sulfate use increased 2 percent in 1975 to 24 percent in 1985, with a six-fold increase in use in recent years. Eleven percent of the newborns who received the drug had adverse reactions. Trichloromethane, an organic solvent which is used to remove adhesive tape from infant skin, is also under study. Because the drug has documented toxicity in cases of occupational exposure, research is focusing on absorption through permeable infant skin. Finally, the pharmacokinetics of tolazoline, a potent vasodilator used in the treatment of pulmonary hypertension, is being investigated in the NICU Network.

Nutrient Requirements of Low-Birth-Weight Infants

NICHD supports research directed toward the nutritional needs of premature and intrauterine-growth-retarded infants. These studies are designed to provide a scientific basis for the provision of optimal nutrition to these tiny infants whose survival depends on nutrition and growth. The metabolic and absorptive capabilities of low-birth-weight babies differ from full-term babies; therefore nutritional strategies must be tailored to meet their unique nutritional requirements. Investigators are searching to define specific diets by which nutritional deficiencies can be prevented or treated in these infants.

In Washington, D.C., Dr. Cecile Edwards and her colleagues at Howard University Hospital and D.C. General Hospital are studying the role of nutrition in low-birth-weight infants born to urban blacks. The incidence of low birth weight births among blacks is 12.5 percent, compared to 5.7 percent for whites. In the nation's capital, 18 percent of black babies are low birth weight; 20.6 percent of births at the Howard University Hospital weigh less than 5 pounds, 8 ounces.

Women in the Edwards' study were from 16 to 35 years of age and were enrolled before the 26th week of their first pregnancy. Eighty-five percent were unmarried. Twenty percent of the women in the study group failed to gain the recommended minimum weight during pregnancy and had serious nutritional deficiencies, reflected in subnormal serum ferritin and folate levels. Maternal prepregnancy weight, maximum maternal weight gain during pregnancy, and weekly weight gain and folate intake during the second trimester were significantly correlated with birth weight. Women who completed the program had significantly larger infants compared to control infants (low-birth-weight incidence of 8.9 vs. 20 percent).

In another study of nutrition for low-birth-weight infants, Dr. Margit Hamosh and her colleagues at Georgetown University in Washington, D.C., continue a multi-year project to assess fatty acids as an energy source. This group has done extensive work on medium-chain triglycerides, which can be more readily absorbed, in the diet of low birth weight infants. Studies now in progress will continue to evaluate the contribution of gastric enzymes to fat digestion and the use of enzyme activity levels in gastric mucosa to diagnose stomach disorders.

Intrauterine Growth Retardation

Infants who have experienced inadequate growth in utero at any stage of gestation are termed growth retarded. Term infants with intrauterine growth retardation (IUGR) usually weigh less than 5 pounds, 8 ounces when they are born. Like the low-birth-weight infants, newborns with IUGR are at a higher risk of dying

before their first birthday than are full-term babies of normal birth weight. NICHD studies of these babies examine biological, epidemiologic, behavioral and social factors related to IUGR, as well as treatment methods.

Researchers at NICHD have also noted differences in growth of black versus white fetuses in an ultrasound study of growth retardation in Alabama. Ultrasound measurements during the second and third trimesters of pregnancy revealed differences in fetal growth related to sex and race. Male infants of both races had larger head and abdominal circumferences than females. Black infants had longer femur lengths than whites at each gestational week examined. Since black infants also were found to have shorter crown-heel lengths at birth, after adjusting for gestational age at delivery, it is possible that the observed difference in body length proportions (longer legs and shorter trunks in black infants than white) is an important factor in understanding the birth weight differences between black and white infants.

Dr. Daniel Edelstone at the University of Pittsburgh is investigating the hypothesis that maternal anemia affects the oxygen supply to the fetus and thus influence its growth. His research suggests that anemia early in pregnancy leads to compensations that enable the fetus to maintain normal oxygenation and growth. When anemia is late in gestation or exceeds the capacity of compensatory mechanisms, the amount of oxygen reaching the fetus is reduced.

The role of fetal growth factors and their relationship to IUGR are being studied by a team of scientists led by Dr. Joseph D'Ercole at the University of North Carolina in Chapel Hill. Using a rat intrauterine model, this group is trying to determine whether fetal growth retardation associated with maternal malnutrition is mediated by a reduction in insulin-like growth factors (IGFs). Preliminary analysis of the study in which the pregnant rat is fasted from day 18-21 suggests that both mothers and fetuses are resistant to fasting and that their growth factors do not drop dramatically as in non-pregnant animals.

Researchers in the institute's Prevention Research Program are conducting studies to help determine whether certain groups of women are at risk of having a baby with IUGR. Staff scientist Dr. Mark Klebanoff and his colleagues are looking at intergenerational links to low-birth-weight babies. Using matched maternal-infant birth certificates in Tennessee, they found that mothers who themselves were low-birth-weight babies were four times more likely to have babies with IUGR, but only 1.6 times as likely to have a preterm baby. Similar patterns occurred in very large studies performed in Sweden and Denmark in collaboration with the World Health Organization. Low-birth-weight patterns between generations are also being studied in research projects in Philadelphia and Providence.

Women who were themselves low-birth-weight babies may require careful monitoring during pregnancy for signs of preterm labor or IUGR. These findings alert the pediatrician to inquire about the mother's weight at birth when a small but otherwise normal-appearing infant has been delivered. The inter-generational link may provide another explanation for difficulty in reducing the incidence of low-birth-weight babies.

Behavioral and Social Risk Factors in Low Birth Weight

A large NICHD study of mothers of low-birth-weight infants has produced preliminary data to support mounting evidence that such adverse health habits as smoking, drinking and illegal drug use pose a major risk factor for low-birth-weight infants. Socioeconomic variables including housing, level of education and environment also were shown to play a role in low birth weight. Researchers headed by Dr. Heinz Berendes, director of the institute's Prevention Research Program, studied the influence of social and behavioral characteristics on the risk of having a low-birth-weight baby. A striking 50 percent of more than 1,000 women who delivered babies in six Washington, D.C., hospitals had low-birth-weight infants. Preliminary analyses indicate that the combined effects of smoking, drinking and illegal drug use account for about 40 percent of the low-birth-weight babies born to this group of inner-city women. Drug abuse alone is responsible for 20 percent of the low-birth-weight risk in this group.

A NICHD-funded study by Dr. Mary Sexton and collaborators at the University of Maryland demonstrated that smoking cessation as late as the third trimester of pregnancy can significantly ameliorate the fetal growth retardation associated with smoking; however, she noted that such behavior change was difficult to bring about. A study completed earlier this year adds disturbing evidence that smoking during pregnancy is the most important single risk factor for low birth weight that could be eliminated by behavior modification. The study of 1,000 black women in the District of Columbia showed that smoking alone accounted for 34 percent of low birth weight. The other factors found to be associated with low birth weight were use of "street drugs", alcohol, and a history of a low-birth-weight or stillborn child. Of the participants--500 cases of low-birth-weight and an equal control group--47 percent were between the ages of 18 and 24; 43 percent had less than a 12th grade education; more than 70 percent had never been married; and 50 percent were below the poverty line. NICHD staff member Leslie Cooper is now working with members of the American College of Obstetricians and Gynecologists and scientists at the National Cancer Institute, National Heart, Lung and Blood Institute, and the Centers for Disease Control to develop a pilot intervention program to help women stop smoking during pregnancy.

Another intervention program, the Better Babies Project in the District of Columbia, is attempting to reduce the incidence of low birth weight by identifying pregnant women in the high-risk areas and intervening with health education and social services. The program attempts to help pregnant women change patterns of smoking, alcohol and drug abuse as part of prenatal care. Some data already suggest that most women can have a normal baby if drugs, for example, are removed early in the pregnancy.

In another study in the Prevention Research Program, Howard J. Hoffman of NICHD, Dr. Robert Goldenburg of the University of Alabama, and colleagues are comparing risk factors for fetal growth retardation in Norwegian and Alabama women with common risk factors of smoking and a previous low-birth-weight infant. They found that women with lower educational levels, poor housing, no access to a car, strenuous physical activity, and high levels of depression, anxiety and stress had higher rates of IUGR births.

The impact of work-related stress on pregnancy is being studied in a project to evaluate medical residents and their spouses. The study, which began in September 1989, will compare the pregnancy outcome of 5,000 female medical school graduates with the non-physician wives of 5,000 male classmates. The study provides the unusual opportunity to evaluate stress without the confounding variables of poverty, low educational levels, and poor environment often found among women considered high risk candidates for low-birth-weight babies.

Prenatal Care

In 1986 an expert panel, appointed by the PHS Committee on Low Birth Weight Prevention, was charged with recommending how much and what types of prenatal care are needed. The NICHD served as the coordinator of this effort. After an extensive study of various aspects of prenatal care, the panel's recommendations were published in a report issued by the U.S. Public Health Service in October 1989. The panel reaffirmed prenatal care as the foundation for improved health of the pregnant woman, the infant, and the family. However, it concluded that ideally care should begin prior to conception, and that every effort should be made to include both the man and the woman in this preconceptional counseling. In order to enable every woman and her family to benefit from the biological and technological advances that have been made, the panel concluded that care should be expanded to include medical and family follow-up up to a year after the child is born. Multi-disciplinary health care teams were not only charged with providing earlier and longer prenatal care, with expanded content, but they were urged to take new approaches to prenatal care delivery.

The panel called for a shift in emphasis from healthy to high-risk expectant mothers. It suggested that many routine tests and procedures are expensive and unnecessary, but it cautioned that routine care must continue to provide health care practitioners the opportunity to monitor patients for development of risk factors during the pregnancy.

The experts identified early and continuing risk assessment, health promotion, and medical and psychosocial intervention and follow-up as the three basic components of prenatal care. Care for all pregnancies should include a complete medical history, education and counseling in healthy behavior and parenting, and treatment of any existing illnesses. Beginning with preconception care, the goals of the panel extended from reduction of preterm births, intrauterine growth retardation, congenital anomalies and failure to thrive, to promoting healthy growth and development, immunization, and health care supervision of the child. Although the panel was aware of the implications for prenatal care providers, governmental agencies, institutions and third-party payers, it did not suggest a change in the basic relationship between the woman and her prenatal care provider. The report urged public and private organizations and agencies to support badly needed research and studies in several areas, in addition to emphasizing the importance of making care available to all women regardless of economic status.

Sudden Infant Death Syndrome

NICHD has a long-standing commitment to research on sudden infant death syndrome (SIDS), commonly known as crib death. SIDS is defined as a sudden, unexpected death that is unexplained after a complete postmortem investigation. SIDS is the leading cause of death in American children between 1 and 12 months of age and is responsible for 7,000 deaths annually. Most of the deaths occur quietly, apparently during sleep. The exact causes of SIDS are still unknown, but scientists appear to have eliminated choking, parental neglect, common infection, and allergy.

Because of the critical need for research, the NICHD SIDS Cooperative Epidemiologic Study was initiated in 1978 to find out how SIDS infants are different from other babies. In a report published in 1987 after a decade of study, 90 percent of SIDS infants were noted to die before they were 6 months old, and 98 percent died before they were a year old. The peak times of death are between midnight and 8 a.m., and more deaths occur during cold weather months. Black infants are nearly three times as likely to die of SIDS as white infants, and babies born to smokers or teenagers, siblings of SIDS victims, or premature or low-birth-weight infants are at higher risk.

The SIDS Histopathology Atlas is expected to be published next year through the Armed Forces Institute of Pathology. It will summarize the findings comparing the 757 singleton SIDS cases and 65 explained death cases which were reviewed by a panel of three SIDS pathologists in the NICHD SIDS Cooperative Epidemiological Study. Eligibility for the extensive study was based on SIDS victims who died between October 1978 through December 1979 in six geographical areas. Two sets of living controls were matched by age to the SIDS cases, with one control group being matched by race (black vs. non-black) and low birth weight. Among the panel's histological findings were pinpoint hemorrhages in the thoracic cavity which were observed significantly more often among SIDS cases compared to explained deaths. Among explained deaths compared to SIDS deaths, there was an increased incidence of fatty changes in the liver and a higher incidence of inflammation of the trachea.

Dr. Ronald M. Harper at the University of California in Los Angeles, has compared the heart rates of infants who later died of SIDS with other infants the same age. SIDS infants were found to have a higher heart rate and decreased heart rate variability. Further analysis revealed that SIDS babies have altered coordination between cardiac and breathing mechanisms. These results support the concept that SIDS infants have immature cardiorespiratory control mechanisms.

The recipient of one of the eight new SIDS research grants awarded this year, Dr. Harper will investigate the organization and physiological measures that define sleep states in normal infants and two groups of at-risk SIDS infants - those who later died of SIDS and siblings of SIDS victims. The project will examine whether SIDS victims die from a failure of mechanisms that normally allow transitions from one sleep state to another and the physiologic signs measured during different sleep states.

In an ongoing study of autopsies, Dr. Charles R. Roe, an NICHD grantee at Duke University Medical Center in Durham, North Carolina, is looking for evidence of abnormal fat metabolism in SIDS victims. A new study beginning this year is examining the role of inherited metabolic disorders as a cause of sudden death in infants. Researchers are looking for abnormal metabolites in infants at risk for SIDS using sophisticated screening technology. The goal is to identify new inherited enzyme defects. These types of genetic defects could be important for neonatal and prenatal screening and nutritional intervention in the future to prevent disease and death. Although only a small fraction of infants is affected, the possibility of prevention and treatment is very high.

Dr. William E. Cameron at the University of Pittsburgh School of Medicine and Dr. Gabriel G. Haddad at Yale University are doing similar studies of respiratory maturation in animals as models for human infant development. Dr. Cameron is examining the development of neural control of the upper airway muscles

with that of the diaphragm during postnatal development, in order to define the role of the motor neurons in shaping breathing patterns. Dr. Haddad's project will investigate the cellular and molecular response to hypoxia in the central nervous system, specifically the brain stem.

Extensive study continues to provide better understanding of the cause, effect, and consequences of abnormal breathing patterns in newborns, the role of mechanisms that arouse infants from sleep, and the development of cardiorespiratory systems.

Birth Defects

More than 250,000 children are born each year with mental or physical disorders; thus birth defects continue to be a leading cause of death in all newborns. NICHD supports numerous research projects designed to identify problems in development and to identify specific genes responsible for birth defects. The projects include clinical and animal models of birth defects and biological research designed to understand normal development processes using molecular genetics and biochemistry.

Central nervous system defects common in newborns make up the largest proportion of potentially fatal birth defects. Spina bifida, one of the most prevalent birth defects, is one focus of the institute's basic research. This defect, in which the spinal canal fails to close completely, occurs in one to two babies in every 1,000 babies born in the United States; the complications claim the lives of 5 to 20 percent of those affected. NICHD-supported studies indicate that of those who do survive the first 24 hours after birth, 75 percent will have severe physical handicaps, while 20 percent will have moderate or severe mental retardation.

Neural tube defects, which include anencephaly and congenital hydrocephalus, are thought to have multifactorial genetic and environmental origins. Therefore, they are considered to result from interaction between a number of inherited genes and unidentified environmental factors. In response to the need for research models, two mouse models have been developed and are being distributed to scientists working in this area. The models--the curly tail mouse mutant and the T-curly tailed mutation--closely mimic spina bifida found in humans. NICHD-supported studies revealed that curly tail mouse spina bifida is due to a delay in the closure of the posterior end of the neural tube of the early embryo. NICHD recently sponsored a research conference on the etiology of spina bifida and other neural tube defects in which the current knowledge base was reviewed and a research agenda generated.

Research on the influence of periconceptional vitamin intake on the incidence of central nervous system disorders such as spina bifida has yielded conflicting results. In an NICHD study

of 1,700 pregnant women in California and Illinois between 1985 and 1987, it was found that vitamin use around the time of conception did not prevent neural tube defects. Other recent studies suggest that vitamins taken by the expectant mother before or shortly after she becomes pregnant protect the infant from neural tube defects. The results of the NICHD study may differ from these other studies because of methodology. For example, the amount of time elapsed between the time of the study and the mother's vitamin use was much shorter in the NICHD study therefore making it more likely that the women were able to recall accurately their vitamin history.

Another area of focus among studies of congenital anomalies is the infants of diabetic mothers. Central nervous system defects and malformations of the heart are much more common among babies born to diabetic mothers. The rate of these defects has risen significantly in recent years and is the leading cause of death in infants of diabetic mothers. Studies supported by NICHD indicate that diabetes-induced embryopathies are caused by one or more factors that disrupt normal intrauterine growth and development.

In another NICHD study, children born as a result of in vitro fertilization (IVF) were found to be at no greater risk of congenital malformation or developmental delays than other children. Researchers examined 83 children born as a result of IVF and 93 non-IVF children comparable in age, sex, race, maternal age, and whether they were a single birth, twin or triplet. All the IVF children were conceived at the Eastern Virginia Medical School in Norfolk between October 1983 and September 1985, while the non-IVF participants were randomly selected from babies born within a 100-mile radius of Norfolk.

The children were examined for both physical and mental development between 12 and 30 months of age. Malformations found in two IVF children and one non-IVF child were not considered statistically significant. Dr. James Mills, NICHD epidemiologist and one of the authors of the report, concluded that the study offers assurance to parents that IVF children should function as well as other children of similar social and economic background.

National Cancer Institute

In 1989, the National Cancer Institute recently funded a study (currently in its fourth year of implementation) designed to reduce smoking among pregnant women, a primary prevention technique for reducing low birth weight and infant mortality.

Numerous studies have established maternal smoking as a principal cause of low birth weight, and in turn, low birth weight as a primary cause of infant mortality.

Dr. Richard Windsor at the University of Alabama Comprehensive Cancer Center in Birmingham, Alabama, and colleagues are studying the effects of active, smoking cessation techniques among low-income women in four clinics operated by the Jefferson County Health Department in the Birmingham, Alabama area.

Preliminary study findings are very promising. In the initial sample of 400 women, cessation rates of 16 percent were achieved in the intervention group, compared with a 4 percent rate in women who did not receive special help with smoking cessation.

A cost-benefit analysis revealed considerable potential health care cost savings, even if just 12 percent of the approximately 350,000 pregnant smokers who annually receive publicly supported health care were to stop smoking. Based on estimates from the Office of Technology Assessment and considering only the babies of the 12 percent of quitters, the total excess publicly supported health care utilization cost of caring for these low-birth-weight babies during the first year of infancy would be over $17 million. Alternatively, intervention costs for materials and staff to be used with the U.S. public health birth cohort of pregnant smokers would be $1.7 million, resulting in a cost-benefit ratio of 1 to 10.

National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI) supports research on infant mortality in the area of neonatal respiratory distress syndrome, a breathing disorder that causes disability and death in premature infants.

Synthetic Lung Surfactant Authorized for Treatment of Neonatal Respiratory Distress Syndrome

A synthetic surfactant was developed by investigators supported by an NHLBI Specialized Center of Research grant to Dr. William Tooley at the University of California, San Francisco, and manufactured by the Burroughs Wellcome Company under the name "Exosurf." Clinical trials of exosurf were begun in 1984, and recent results have shown that treatment of premature infants with the synthetic surfactant is associated with significant improvements in lung function and a reduction in mortality from neonatal RDS. Although Exosurf has not been approved formally by the Food and Drug Administration (FDA), it has been released by the FDA under a new program to speed potentially life-saving treatment to patients critically ill with conditions for which no satisfactory standard therapy exist. Successful treatment with Exosurf results in reduced periods of mechanical ventilation for infants with RDS, thereby decreasing the chances of complications from that procedure. Future work will involve testing the efficacy of synthetic surfactant in the treatment of other respiratory conditions of newborns, including pneumonia and acute lung injury.

Surfactant Differences May Explain Differences in Prenatal Lung Maturation and Incidence of Neonatal RDS in Blacks and Whites

Black infants are known to have lower rates of RDS than white infants, despite the higher incidence of premature and low-birth-weight infants among blacks. Investigators supported by an NHLBI Specialized Center of Research grant to Dr. Mary Ellen Avery, Brigham and Women's Hospital, Boston, Massachusetts, are working with scientist from Nigeria to explore the possibility that there is a difference in lung surfactant between the races and that this difference might help to explain the lower rates of RDS in blacks.

Initial studies using probes for genes that code for the proteins associated with lung surfactant have revealed racial differences in the genetic patterns for one of the surfactant proteins. The finding is preliminary and needs to be confirmed in further studies. If confirmed, however, it may help to explain the earlier maturation of the lungs of black infants and the rarity of RDS among premature black infants weighing more

than 1,500 grams. Moreover, if accurate and reliable genetic markers of lung maturation can be determined, they should enhance the ability to predict which individuals, either black or white, at risk of delayed lung maturation.

National Institute of Neurological Disorders and Stroke

Brain hemorrhage affects nearly one half of low-birth-weight infants and is a significant cause of mortality and morbidity in newborns. The National Institute of Neurological Disorders and Stroke (NINDS), is the focal point for research on the causes and prevention of this serious disorder.

Dr. Henrietta Bada, an NINDS grantee at the University of Tennessee in Memphis, has investigated the use of the drug indomethacin to prevent brain hemorrhage in infants. During a controlled trial with 120 low-birth-weight infants, Dr. Bada found that babies treated with indomethacin experienced less severe hemorrhaging and had reduced levels of circulating prostacyclin, a compound found in the blood that contributes to increased blood flow and helps prevent blood clots.

Because these findings point to indomethacin as a potential preventive of brain hemorrhage, NINDS is funding further evaluation of this promising drug. Grantee Dr. Laura Ment of Yale University in New Haven, Connecticut, is conducting a multi-center, controlled trial of indomethacin in low-birth-weight infants. Her study will assess long-term health benefits of the drug, as well as its efficacy in preventing and limiting cerebral hemorrhage.

National Institute of Allergy and Infectious Diseases

Each year, 5 to 10 million of the world's infants and children die of gastrointestinal diseases, largely the result of bacterial and viral infection. Singling out the organisms that cause these infections and identifying methods to prevent them is a mission of researchers whose work is conducted and supported by the National Institute of Allergy and Infectious Diseases (NIAID).

Mother's Milk as a Weapon Against Bacterial Disease

Diarrhea caused by bacterial infection takes the greatest toll among gastrointestinal-related deaths in infants. Although researchers have already established a positive association between breast feeding and reduced incidence of diarrheal disease, how human milk inhibits microbial activity is still unclear. Furthermore, scientists have yet to define the full spectrum of diarrhea-causing microbes susceptible to the effects of breast milk.

NIAID researcher Dr. Stephen A. Dolan and his co-workers at the University of Missouri-Columbia in Columbia, Missouri, undertook a study to determine which bacteria respond to milk's inhibitory effect and whether different strains of these bacteria react similarly. The researchers obtained milk from seven nursing mothers who had given birth 1 week to 3 months previously. Multiple strains of four diarrhea-causing types of bacteria were then cultured with either the milk whey, commercial infant formula, or soy broth. For most of the strains tested, milk whey proved to be far more potent than formula in reducing bacterial multiplication. On the other hand, in assays of the bacteria *Campylobacter jejuni*, the researchers found that formula was the stronger inhibitor.

Dr. Dolan's work shows the value of exploring methods to increase the protective effects of breast milk, either by immunizing the mother or providing her with nutritional supplements. The immunization approach is supported by animal studies, particularly a recent study that demonstrated the feasibility of protecting a newborn calf from cholera by immunizing its mother. In addition, Dr. Dolan's work study highlighted the potential of improved infant-feeding formulas. For example, in communities with a high prevalence of bacteria not susceptible to the protective effects of breast milk, supplemental feeding with formula developed for enhanced inhibitory capabilities could be of immense benefit to newborns.

Virus Related to Animal Pathogens May Cause Illness In Human Babies

To devise a strategy for preventing life-threatening disease, scientists must first find the microbe responsible for infection. In cases of diarrhea caused by a virus, the process for identifying the culprit can be extremely difficult for a number of reasons: the viral particles themselves tend to be too small or of insufficient quantity to be detectable; many types of virus do not grow in tissue culture; and the immune system responds differently to each type of pathogen, making it difficult to predict at what point in the infection process the body will secrete the viral particles scientists need for study.

Dr. Robert Yolken at the Johns Hopkins University School of Medicine in Baltimore, Maryland, specializes in diagnosing viral diseases. His most recent findings, in research contracted by NIAID, involve members of the viral genus *Pestivirus*, known to cause intestinal disease in animals, but never documented as a cause of illness in man. In animal studies, these microbes have been known to cross bovine placenta and infect the fetal calf.

Rather than attempting to detect the virus itself, Dr. Yolken devised an assay to detect the viral antigen, a substance in the invading virus that triggers the body's immune system to produce antibodies, which protect against the virus. When an antibody recognizes a particular antigen, the body's immune mechanisms stimulate a chemical reaction, serving as an indicator that a viral antigen is indeed present.

The Indian Health Service Hospital at Whiteriver, Arizona, provided Dr. Yolken's study population, which consisted of 128 babies under 2 years of age with diarrhea. Previous researchers found that half of the diarrhea cases in this group could not be attributed to a known organism. Under a study protocol that involved a complex series of assays, which included running control samples consisting of antibodies against several other diarrhea-causing viruses, Dr. Yolken found that of the 128 babies in the study, samples from 30 tested positive for bovine *Pestivirus* antigen.

Most of the babies who tested positive were less than a year old, and compared to the rest of the group, more required hospitalization. Dr. Yolken found that a large portion of the group also had respiratory complications, a factor that not only serves as a possible diagnostic indicator, it suggests that an infection previously unknown in humans could have severe consequences for human infants.

National Institute of Environmental Health Sciences

There is ample scientific evidence demonstrating that children during prenatal and postnatal development are particularly sensitive to environmental agents. During the pre- and postnatal period the child is dependent on the nutrients provided by the mother, either through the placenta prior to birth or through breastfeeding after birth. Thus, the National Institute of Environmental Health Sciences (NIEHS) is concerned about the effects of environmental agents on the mother and child during development, as well as the changes that occur in the metabolism of environmental agents during pregnancy. The NIEHS is particularly concerned about the mechanisms through which an environmental agent causes toxicity.

The N-nitroso compounds (NNO) are a class of ubiquitous environmental pollutants. These compounds are present in things like side-stream cigarette smoke, bacon, food preservatives, cosmetics and shampoos. Thus, there are few, if any, humans unexposed to these pollutants. Animal models have demonstrated that NNO compounds are developmental toxicants causing injuries to the central nervous and musculoskeletal systems. Dr. Elaine Faustman, an NIEHS grantee at the University of Washington in Seattle, is developing an <u>in vitro</u> model to study the mechanism of toxic effects of these compounds on developing systems.

Polynuclear aromatic hydrocarbons (PAHs) are another class of major contaminants found in industrial and urban environments. Specific PAHs are found in most smokes. Thus, human exposure to PAHs from various sources and activities is extensive. It is known from animal studies and epidemiological studies of women who smoke cigarettes during pregnancy that PAHs are toxic and may be teratogenic agents. The mechanisms for these and other effects are not well understood. NIGHS grantee Dr. Mrinal Sanyal at Yale University in New Haven, Connecticut, has initiated a study to determine how PAHs may be teratogenic. Initial studies suggest that smoking alters key enzymes that metabolize environmental chemicals to products capable of placental or fetal toxicity. These studies are important because previous hypotheses suggested that these enzymes were involved in chemical detoxification and thereby protective of the fetus.

Another potential hazard to the developing fetus revolves around modern agricultural practices, which include intensive use of pesticides and other types of agricultural chemicals for enhancing crop yield. Many of the pesticides used are thought to have teratogenic/mutagenic potential. Human exposure to agricultural chemicals can occur through ground water and pesticide residues on food, as well as through air-borne exposure at the time of application. Dr. James Beaumont, an NIEHS grantee at the University of California, Davis, is conducting an epidemiological study in the San Joaquin Valley in California to assess possible relationships between fetal death and pesticide

exposure during pregnancy. One specific endpoint being followed in this study is the potential correlation between low birth weight and pesticide exposure.

NIEHS scientist Dr. Allen Wilcox is using data from a prospective study of early pregnancy to explore factors that affect fertility. In a series of studies, Dr. Wilcox and his co-investigators have found that women exposed prenatally to their mother's cigarette smoking are substantially less fertile as adults. Methods for detecting early pregnancy developed by NICHD grantee Dr. Robert Canfield at Columbia University in New York and used in the NIEHS study, may provide a sensitive means for detecting reproductive effects of some environmental hazards. Dr. Wilcox and his colleagues also observed for the first time that women who consume greater amounts of caffeinated beverages take longer to get pregnant. He is now collaborating in a study correlating the time it takes to get pregnant and with caffeine consumption among women in an <u>in vitro</u> fertilization program.

Other studies are planned to examine in detail the reproductive performance of women who were exposed <u>in utero</u> to diethylstilbestrol (DES). These women have been identified as having a high frequency of abnormalities of the reproductive tract. The study cohort is from the largest controlled clinical trial of DES use for pregnancy support; thus, it comes with a natural comparison group, and should allow more valid conclusions than have been possible previously.

National Institute of Arthritis and Musculoskeletal and Skin Disease

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) research focuses on several potentially fatal diseases that affect the bones, joints, muscles, or connective tissues or infants. The advances described here include research on the inherited blistering skin disease called epidermolysis bullosa, or EB, and on osteogenesis imperfecta (OI), a disorder of connective tissue in which affected infants are abnormally susceptible to bone fractures.

In research on EB, Dr. D. Martin Carter at the Rockefeller University in New York, in collaboration with the Food and Drug Administration, led a multi-center trial to test the efficacy of the drug phenytoin (an anticonvulsant) for the treatment of recessive dystrophic EB. This form of EB is quite severe; many times almost all body surfaces are covered by blisters and may be virtually devoid of normal skin. Scarring of the mucous membranes in the esophagus interferes with passage of food into the stomach, causing anemia, malnutrition, and retarded growth. Because past research had suggested that a phenytoin decreases an enzyme that is abnormally produced in EB, it was hypothesized that this drug might be effective for patients with the disease.

Overall, the trial failed to show a therapeutic benefit from phenytoin in patients with EB. The researchers found no difference in the size or number of blisters when the patients received phenytoin or when they were on a placebo. Phenytoin was effective only in reducing the number of tissue erosions seen in the patients. Because of the toxic side effects of this drug, the researchers could not recommend the use of phenytoin unless a patient on the drug showed a marked improvement. Other candidate drugs for EB now are being evaluated in animal models to find a more effective treatment for this disease.

In other EB research, the NIAMS-supported National EB Registry was used to search for gene defects in patients with recessive dystrophic EB. Dr. Jo-David Fine at the University of Alabama in Birmingham, who directs one of the centers of the registry, used genetic technology to show an association between patients with this type of EB and their tendency to inherit a particular gene cluster more often than do persons without the disease. The researchers are continuing to use the registry to study additional patients to determine the precise gene mechanism(s) underlying this disease.

NIAMS-supported research Dr. Jeffrey Bonadio at the University of Michigan, Ann Arbor, has applied new techniques to analyze gene mutations in infants born with perinatal lethal OI or OI type II. These newborns have very fragile connective tissue because of faulty production of collagen, a protein which contributes to bone strength and organization. These babies are

extremely fragile and experience multiple bone fractures even in utero. Dr. Bonadio found that the defective collagen in perinatal lethal OI results from an amino acid substitution in the gene, which alters the way the protein is assembled. The techniques of polymerase chain reaction (PCR) that were first applied to studying collagen genes in this investigation can be used to study the other types of OI and will allow more rapid determination of the structure and function of the complex collagen molecule.

Division of Research Resources

The Division of Research Resources (DRR) supports a wide range of research aimed at understanding the causes of infant mortality. A major effort at General Clinical Research Centers (GCRC's) is focused on examining the complications of premature birth.

GCRC's provide the research infrastructure for multidisciplinary studies on both children and adults. Specifically, they provide patient research facilities, computerized data management and analysis, as well as research nurses, dietitians, biostatisticians, and specialized laboratories for the translation of basic and clinical research into medical practice.

It has been established that infants born prematurely often develop bleeding in the brain. The clotting and inflammation that result can clog the passages that allow fluids to drain naturally out of the brain's ventricles. This can lead to hydrocephalus, commonly called water on the brain. As fluid accumulates, brain tissue is squeezed, and, unless the pressure can be relieved, damage may result.

A new test that exactly measures the volume of fluid in brain ventricles has been developed by DRR grantee Dr. Benjamin Brann and his associates at the University of New Mexico GCRC in Albuquerque. Ultrasound images of ventricles are traced into a computer. Computer software written by Dr. Brann and his colleagues calculates the ventricle size and computes the volume of fluid. This volume is compared to others calculated from previous images, allowing fluid accumulation to be easily detected.

According to Dr. Brann, more than 70 infants have been successfully monitored with this new technique. More than 20 showed signs of hydrocephalus. Without the computer tracking technique, ultrasound images must be visually compared by the physician, who then must estimate whether the ventricles are getting bigger.

Dr. Brann notes that an exact record of fluid accumulation showing trends is important because about half of all cases of hydrocephalus regress without damaging brain tissue. Surgery to drain ventricles is particularly dangerous when done on premature infants. Therefore, physicians need to identify the newborns at risk of being injured by the accumulation of fluid. Careful monitoring of these patients with ultrasound and computer analysis of the images can provide an exact record of fluid in infants who have experienced brain bleeding, Dr. Brann concludes.

Another concern with premature babies is that they are often deficient in surfactant, a substance necessary for lung expansion and tissue elasticity. DRR grantee Dr. T. Allen Merritt and his

associates have been administering natural human surfactant to very premature infants at risk for developing respiratory distress syndrome (RDS), which is caused by this deficiency. According to Dr. Merritt, this treatment lessens the severity of pulmonary illness, which often follows RDS, and prevents more RDS-associated deaths than does conventional ventilatory therapy alone.

In collaborative studies at the University of California GCRC in San Diego, the University of Helsinki and the Hospital of the Midwifery Institute in Helsinki, Finland, human surfactant was sprayed into the lungs of about 30 very premature infants who were at risk of developing severe RDS. The treatment significantly decreased morbidity and mortality among these infants compared to a similar group that did not receive the treatment.

Premature infants are also susceptible to streptococcal infections, particularly those caused by group B beta-hemolytic streptococci (GBS). These bacteria cause early onset disease, characterized by progressive respiratory failure, pulmonary hypertension, and cardiovascular collapse. Recently the toxic components of a poison generated by these bacteria were identified, clearing the way for the development of methods to treat or prevent this disease, which is fatal in a third of affected premature infants.

NATIONAL CENTER FOR NURSING RESEARCH

The National Center for Nursing Research (NCNR) supports research and research training on methods to reduce infant mortality by developing better nursing techniques to help maintain or improve health during pregnancy, prevent preterm birth and low birthweight, provide optimum care for preterm and low birthweight infants, and promote infant health.

Dr. David L. Olds, of the University of Rochester Medical Center in Rochester, New York, is studying the effects of prenatal and postpartum nurse home visits on the health and well-being of poor pregnant women living in an urban area and their first-born children. The NCNR grantee and his research team are seeking to determine whether nurse home visits can help prevent many problems that contribute to infant mortality, such as prematurity and low birthweight, growth and nutritional problems, accidents, acute infectious illnesses, and child abuse and neglect.

The investigators will compare two groups of about 700 black women during pregnancy. Both groups will receive transportation for prenatal care, but one group will also receive regular prenatal visits from a nurse. These visits will be aimed at reducing cigarette smoking, drinking, and non-prescription drug use during pregnancy, and fostering healthy weight gain. The investigators hope to achieve a higher rate of treatment for infections or hypertensive disorders, increased preventive care and fewer emergency-room visits, more support from family members and friends and less depression and anxiety in the mothers in the home visitation group.

For two years after delivery, one group of 250 women will receive regular postnatal visits from a nurse as well as sensory and developmental screening for the children. The investigators will assess the effects of the nurse visits on the mothers' child care practices, as well as on their mental-health functioning, their use of health and human services, the number of unintended pregnancies, and their reliance on welfare. These women will be compared to a group of 500 women who after delivery receive only screening services for their children.

The researchers will look at whether prenatal and postpartum nurse home visits will reduce government expenditures by helping to avoid the high costs often associated with maternal and child dysfunction.

This study replicates a previous one by Dr. Olds, done in a rural area, which involved nurse home visits to young white pregnant single women and their first-born children. That study showed that nurse home visits in this type of population can help prevent many problems which would place infants at higher risk of mortality.

Outlook

While it is disappointing that the nation did not reach the 1990 goal set for infant mortality at the beginning of the decade, significant progress was made toward that achievement. The U.S. had an all-time low mortality rate in 1988, and remarkable progress was made over the past 10 years in our ability to save the lives of premature and sick newborns.

Research directed specifically at reducing infant mortality has intensified in recent years. This research has led to advances in medicine and patient care as well as yielding powerful new technological tools with which to combat the problem.

Applying these advances and employing the new technological tools ensures that much progress will be made in the coming decade, with the hope that the goals set for infant mortality for the year 2000 can be realized.

* U.S. Government Printing Office : 1990 - [illegible]