Effect on Breastfeeding of Pacifiers and Bottle Feeding

Summary

Statement of the Problem

Healthy People 2000 goals state that 75 percent of women in this country will initiate breastfeeding and 50 percent will continue to breastfeed at 5–6 months. Currently, about 59 percent of women initiate breastfeeding and as few as 20 percent are still breastfeeding at 6 months. Proper sucking technique is believed to be critical to establishing breastfeeding and preventing early breastfeeding problems. Observational studies of pacifier use indicate a possible association with shorter breastfeeding duration; however, the effects of pacifier use and artificial nipple use during bottlefeeding or breastfeeding have not been evaluated with rigorous scientific methods. Given the numerous health benefits of breastfeeding, scientific investigation of the effect of early artificial sucking experiences on the ability of newborns to breastfeed successfully is of profound relevance and importance to maternal and child health in the United States.

Research Questions or Hypotheses

The specific aim of this study is to minimize obstacles that prevent the successful establishment of breastfeeding. This study is designed to ascertain the effect of artificial nipple experiences (pacifier use and bottlefeeding) on the successful establishment of breastfeeding. Interaction between exposure to artificial sucking experiences and successful breastfeeding are hypothesized to occur, placing infants who experience both early pacifier use and bottlefeeding at
highest risk for adverse breastfeeding outcomes, and those exposed to later pacifier introduction and no supplemental feeding at lower risk.

The specific study hypotheses are as follows:

1. Early pacifier use (within 2–5 days of birth) as compared with no pacifier use by breastfed infants is associated with reduced breastfeeding duration and increased breastfeeding complications during the first month of life. Specifically, it is hypothesized that early pacifier use (a) decreases the duration of exclusive breastfeeding; (b) decreases the duration of overall breastfeeding; (c) increases the incidence of maternal breastfeeding complications (including nipple trauma and engorgement); (d) increases the incidence of infant breastfeeding complications (including increased postnatal weight loss, increased time until birthweight is regained, and incidence of feeding-related hyperbilirubinemia); (e) decreases the chances that the mother will attain her personal breastfeeding goal; and (f) increases the incidence of early supplemental feeding during the first 2 weeks of life.

2. Early pacifier use (within 2–5 days of birth) compared with late pacifier use (after 4 weeks of age) by breastfed infants is associated with reduced breastfeeding duration and increased breastfeeding complications during the first 6 months of life. It is hypothesized that early pacifier use (a) decreases the duration of exclusive breastfeeding; (b) decreases the duration of overall breastfeeding; (c) increases the incidence of maternal breastfeeding complications (including nipple trauma and engorgement); (d) increases the incidence of infant breastfeeding complications (including increased postnatal weight loss, increased time until birthweight is regained, and incidence of feeding-related hyperbilirubinemia); (e) decreases the chances that the mother will attain her personal breastfeeding goal; and (f) increases the incidence of early supplemental feeding and the number of supplemental feedings required in the hospital and during the first 2 weeks of life.

3. In breastfed infants who require early supplemental feedings, bottlefeeding (as compared with cup feeding) is associated with reduced breastfeeding duration and increased breastfeeding complications. It is hypothesized that early supplemental bottlefeeding in breastfed infants (a) decreases the duration of exclusive breastfeeding; (b) decreases the duration of overall breastfeeding; (c) increases the incidence of maternal breastfeeding complications (including nipple trauma, engorgement, early breastfeeding cessation [while in the hospital], and longer postpartum length of stay); (d) increases the incidence of infant breastfeeding complications (including increased postnatal weight loss, increased time until birthweight is regained, increased incidence of feeding-related hyperbilirubinemia, lower rates of full breastfeeding at discharge, and increased rates of required early followup [within 48 hours]); (e) decreases the chances that the mother will attain her personal breastfeeding goal; and (f) increases the incidence of early supplemental feeding.

Study Design and Methods

This randomized, single-blinded, clinical trial seeks to evaluate in a sample of breastfed infants the effects of artificial nipple exposure on the incidence of breastfeeding complications and breastfeeding duration. Healthy breastfed infants of participating women will be randomized to two pacifier study groups: (1) Pacifier use beginning after hospital discharge (within 2–5 days of birth), or (2) pacifier use beginning during the fifth week of life. Participating infants who require supplemental feedings as part of their newborn care will be randomized to cup feeding or bottle-feeding in the supplemental feeding intervention.
Interviews conducted during postpartum hospitalization, feeding observations, chart reviews, and 6 months of prospective followup will be used to ascertain differences in breastfeeding complications and duration.

Population Description and Sampling Plan

Pregnant women will be recruited prenatally to participate, and informed consent will be obtained. Approximately 20 percent of the women participating in this study are being recruited from minority and/or impoverished populations.

Analysis Plan

Descriptive statistics will be prepared, and the normality of continuous variables will be checked. Comparability of the intervention groups will be analyzed with the chi-square test, Fisher's Exact Test, Student's t-test, and the Wilcoxon test as appropriate. Variables for the comparison will be prespecified. Three primary outcome comparisons will be made: (1) The effect of cup feeding versus bottle feeding on the duration of breastfeeding among those who required supplemental feeding while in the hospital; (2) the effect of early versus late pacifier introduction on the duration of breastfeeding to 6 months; and (3) the effect of early versus no pacifier introduction on the duration of breastfeeding to 1 month (early group versus the late group in which pacifier use does not begin until the fifth week). Survivorship methods (including the Kaplan-Meier regression model and the Cox proportional hazards model) will be used to adjust for possible confounding variables. Secondary analyses will examine the effects of both interventions simultaneously.

Pre-Award Evaluation

Originality and Importance

Rates of breastfeeding initiation and continuation are disappointingly low in the United States. This project is designed to address one reason for poor continuation of breastfeeding: "Nipple confusion," brought about by the early (in the first few days of life) introduction of pacifiers and/or bottle feedings. The investigators postulate that under these circumstances an infant learns improper sucking techniques, which interferes with breastfeeding. The infant is then less able to empty the breast effectively, which may lead to difficulty in establishing an adequate milk supply or other complications. When this happens, the infant may be given more supplemental feedings, which may only exacerbate the problem, leading to early cessation of breastfeeding. This biological mechanism makes intuitive sense and is in accord with clinical experience.

Regional and National Significance

The United States is far from achieving the Surgeon General’s targets for breastfeeding initiation and duration, and the trends are actually worsening. Research that might improve breastfeeding success is important to public health and Maternal and Child Health Bureau (MCHB) goals. Therefore, this project has regional and national significance.

Scientific and Technical Merit

The proposed randomized, factorial design is the appropriate experimental procedure for testing the investigators’ hypotheses. Randomization will be stratified by insurance source to ensure that differences in socioeconomic status are accounted for in
the treatment groups. The research design is attractive because it requires minimal interference with usual practices (only half of the parents will have to delay the introduction of pacifiers, and alternative ways of comforting their infants will be provided). No change in parental behavior is required for the bottle/cup portion of the study, because this applies to supplemental feedings given by hospital staff.

It is important to remember that there are numerous other reasons for early cessation of breastfeeding. These include lack of cultural support for breastfeeding, lack of adequate maternity leave, lack of child care at or near the workplace, and lack of facilities for pumping breast milk in the workplace. These other reasons may be as or more important than “nipple confusion,” and the investigators must detect an effect of their treatments within this generally unsupported milieu.

Power calculations are provided, but unfortunately no data are provided to support the expected differences described for the supplementation or the pacifier. This renders these calculations less persuasive than they could be.

It is not clear why secondary analyses are required for investigating the postulated interactive effects. Such effects can be obtained as part of the overall data analysis strategy by simply categorizing the infants by their exposure to supplemental feeding and the type of supplemental feeding (nested design).

The single-blinding is questionable. How can the interviewer be blind when the subjects are asking questions about supplemental feeding and breastfeeding? The sample size is well-justified. However, crossover may decrease the expected differences among the supplemental feeding groups and early and late use of pacifier groups.

The research will be carried out in a community hospital with 2,800 deliveries each year. This hospital includes a high proportion of women who deliver healthy infants and choose to breastfeed them. The data collection forms are already available. The principal investigator has developed these for another ongoing research project; thus, no investment is needed for their development.

The principal investigator, Dr. Cynthia Howard, is a pediatrician with additional training in public health. The other members of the proposed staff are well-qualified for their roles.

The personnel commitment for the statistical analysis seems excessive for a project that is essentially a chart review plus several brief telephone interviews to ascertain whether and to what extent breastfeeding is continuing. Similarly, the personnel commitment for “vision” and general “consultation” seems excessive.

There are no concerns regarding the use of human subjects. Subjects will receive normal pediatric care. Those instructed to delay the introduction of a pacifier will receive instructions in comforting a crying baby.

This study has a plausible, biologically based hypothesis and an appropriate, realistic design. Study findings will likely lead to a change in hospital practice and how parents are counseled about comforting their infants. These changes may result in an improvement in the duration of breastfeeding. The major weaknesses of the study are the excessive budget and the lack of persuasive power calculations. Nevertheless, the recommendation is for approval.
Summary

Statement of the Problem

Regular developmental screening of the 5 to 15 percent of the population of infants ages newborn to 3 years who are at risk for delay is widely promulgated but rarely achieved. This is increasingly true as primary care providers face cost-containment measures, including staffing reductions and higher patient volumes. Screening approaches that use parent-completed developmental questionnaires such as the Ages and Stages Questionnaire (ASQ) offer valid and reliable screening and opportunities for parent involvement, in addition to freeing staff to meet other professional duties. However, the use of these tools as reliable screening instruments needs to be assessed in low-income urban settings with high-risk families in unstable housing situations.

Research Questions or Hypotheses

The goal of this randomized, clinical controlled trial is to examine the feasibility of three different approaches to the periodic screening of at-risk children within the context of a public health agency/primary care clinic. Three approaches are to be compared: (1) The Denver Developmental Screening Test (Denver II), to be administered by a provider, plus an initial ASQ, which will be mailed to parents one time only; (2) the ASQ alone, which will be mailed to parents at certain stages of their child’s development; and (3) the ASQ mailed to parents (same frequency as in group 2), plus a monthly parenting newsletter and toy.
Six hypotheses are proposed:
1. The percentage of initial screening by ASQ will be equal to or better than the rate of initial assessment by providers;
2. Patient retention will be equal or higher in groups 2 and 3 than in group 1.
3. The percentage of ongoing screening in group 3 will be greater than in group 2;
4. In a child who has been screened with both the Denver II and a one-time ASQ, there will be concordance on suspected delay.
5. With ongoing screening, cross-group comparisons will show that the rate of “suspected delay” screening in the ASQ groups (groups 2 and 3) will be equal to or greater than in group 2.
6. Certain subgroups (defined by demographic and/or risk factors) may respond better than others to an ASQ approach.

**Study Design and Methods**

This randomized clinical controlled trial seeks to compare three approaches to developmental screening within the context of a public health agency/primary care clinic. Study subjects are referred to the Infant-Child Health Assessment Program (ICHAP), which randomizes the subjects to one of three group formats for screening.

For subjects enrolled in group 1, the Denver II screening will be completed by the primary caregiver when the child is 6, 12, 20–24, and 30 months of age. In addition, the ASQ will be mailed one time to the parents. Parents of children in group 2 will receive only the ASQ when their child is 4, 6, 12, 16, 18, 20, 24, 30, and 36 months of age. The parents of children in group 3 will receive the ASQ with the same frequency as those in group 2, but will also receive a monthly newsletter plus a toy. For the latter two groups, ICHAP handles all subsequent outreach to the family, conducts the mailing and scoring of ASQs, and submits feedback to the pediatrician. For those in group 1, the pediatrician periodically administers the Denver II.

**Population Description and Sampling Plan**

The project will be implemented at two sites selected because of their large at-risk populations: one site has a predominantly black population, the other a predominantly Hispanic population.

Families with at-risk children ages 3–18 months who attend a pediatric primary care center and are eligible for ICHAP (New York’s P.L. 99–457, Part H, Child Find program) are offered enrollment by their pediatrician. Approximately 400 children will be enrolled, with an estimated 30 percent loss to followup.

Eligibility for the study is based on the following criteria: (1) The child has one or more risk factors, based on a list by ICHAP of New York; (2) the child has no known developmental delay; (3) the child is between 3 and 8 months of age; (4) the caregiver speaks English or Spanish; and (5) the caregiver can be contacted by telephone (either a personal phone or a friend’s phone).

**Analysis Plan**

For each of the three groups, the project will examine the rates of initial and followup screenings obtained, the rate of positive screenings, and the percentage of at-risk children who remain engaged in care. Additionally, the degree to which income, maternal education, risk status, and other factors predict outcomes within the three groups will be analyzed. This project will also explore the feasibility of a public health/primary care/parent partnership that could lead to a cost-
efficient model adaptable for wider use in Part H at-risk programs.

Preliminary data analysis will start 3 months after the beginning of enrollment and will continue through the followup period to monitor progress.

**Pre-Award Evaluation**

**Originality and Importance**

The main goal of the proposed research is to determine whether the use of a parent-completed developmental questionnaire will be a reliable screen for use in low-income urban areas characterized by high-risk families and unstable housing situations. The proposed study involves a randomized clinical controlled trial that seeks to compare three approaches to developmental screening within a public health agency/primary care clinic context. The proposal addresses a research question of importance to the Maternal and Child Health Bureau, and the investigators contend that answers to the research questions posed by the study could support the utility of a public health/primary care strategy and help lead to a cost-efficient model adaptable for wider use in at-risk programs.

**Regional and National Significance**

The proposed research has the potential to provide important information to the MCH community about approaches to developmental screening in public health clinics. The degree to which income, maternal education, risk status, and other factors predict outcomes within high-risk families is of great importance to the lives of children in unstable situations. All of these factors affect the communities in which these families live. The prospective findings are likely to have a high degree of applicability in the delivery of health care. Clearly, this research project has both regional and national significance.

**Scientific and Technical Merit**

This application, initially reviewed at the MCHB Research Program’s review cycle in November 1996, was deferred at that time, pending clarification of two issues. The reviewers asked for a more comprehensive and detailed data analysis plan that would include the suggested analyses on racial/ethnic data. As suggested by the review panel, the investigators have sought statistical consultation and have revised their data analysis plan to more adequately address the research questions. The revised analysis plan is much improved, and a consulting statistician has been included as part of the research team.

The reviewers requested additional information on the reliability and validity of the ASQ with a low-income Hispanic population (similar to the population to be included in the proposed research). The researchers have provided additional information that, although based on small samples, appears promising enough to justify a more intensive data collection effort as proposed in this study.

As noted in the earlier review, the budget is appropriate but could be reduced. The sample informed consent form submitted by the researchers is still unclear in some areas. For example, the statement that “the benefit of the study will be to help assure that my child receives these assessments regularly” may be misleading. The review committee also believes that it is important to review the Spanish-language version of the consent form (which was not submitted for review), because literal translations can be confusing.

The reviewers judged the application to be very well written and technically strong. The research plan is logically and sequentially presented, and its details
are justified with economy and clarity. The study will have broad policy implications for infant screening practices. A particular strength of the proposed research is that it builds on a close collaboration between a public health agency and primary care providers. The use of the ASQ is another strength, since this scale is designed for parent response and has gained acceptance in the early intervention community. The research questions that address whether receiving a parent newsletter would facilitate children/parents remaining in their medical home and would encourage parents to complete the screening instruments will potentially provide useful information. The researchers have been very responsive to the concerns raised by the review panel, and the issues have been clarified. Approval is recommended, with the condition that funding should not proceed until the MCHB Research Program receives a copy of the Spanish-language version of the informed consent form.
Home Nursing to Avoid Pediatric Hospitalization

Summary

Statement of the Problem

Hospitalization accounts for almost 50% of child health expenditures. Adverse psychosocial effects of hospitalization are broadly recognized. Studies indicate that hospital admission is often highly dependent on physician discretion and that services provided to many hospitalized children could be delivered in alternative settings. The study team proposes a home nursing enhancement of primary care (HNEPC) as a new alternative to hospitalization for children who have common illnesses.

Research Questions or Hypotheses

The purpose of this study is to evaluate the home nursing program in Monroe County, New York. The main study phase will address the following questions:

1. What is the potential for implementing HNEPC on a community-wide basis?
2. How well will HNEPC be accepted by families and providers?
3. What is the net impact of HNEPC on hospitalization for episodes eligible for randomization and on overall community hospitalization rates?
4. What will be the cost of care for episodes randomized to different groups?
5. Will quality of care for illness episodes in the treatment group be equal to or better than in the control group?
Study Design and Methods

Following are the essential characteristics of the HNEPC design: (1) Capacity to deliver services comparable to those provided to hospital inpatients for selected common illness episodes; (2) immediate accessibility; (3) ability to adjust to the unique and changing needs of different families and illnesses; (4) the unique opportunity in home-based interventions to promote health-enhancing behavior; and (5) integration in both primary care and hospital care systems.

Phases of this study include preparation (in which the intervention will be piloted), research pilot, main study, and analysis. Funding for the preparation phase has been secured.

During the research pilot, 66 additional illness episodes will be cared for with HNEPC, and research instruments will be piloted in field situations and refined.

During the main study phase, 1,590 patients with acute illness episodes who present to the hospital emergency department will be randomized to either the treatment or control group. HNEPC will be one option available for the management of episodes in the treatment group, whereas only the usual options (inpatient or family home care) will be available for those in the control group.

To address the efficacy and effectiveness of the intervention in terms of quality of care, outcome variables to be measured will include number of illness days, amount of time needed to return to normal activity, medical record review, impact of illness on family, family/nurse/provider satisfaction with quality of care, and subsequent use of hospitalization. Potential confounding variables to be assessed include socioeconomic variables and severity of illness.

Population Description and Sampling Plan

Of the expected 9,399 patients ages 1 month to 19 years in the likely clinical groups presenting to the emergency department, a total of 1,767 will be eligible for randomization based on meeting the inclusion criterion. After refusals are accounted for, a total of 1,590 patients will be included, with 795 assigned to the treatment group and 795 to the control group. After patients are accepted in the randomization component of the study, their care will be determined by joint decision of the provider and the family. HNEPC will be available only in the treatment component of the study.

Analysis Plan

Data analysis plans include descriptive analyses and cost-benefit analyses, plus bio-equivalence, analysis of variance (ANOVA), and logistic regressions for the randomized clinical trial component.

Pre-Award Evaluation

Originality and Importance

This proposed 3-year study would evaluate Home Nursing Enhanced Primary Care (HNEPC), an intervention that would be implemented in place of inpatient hospitalization. The researchers propose to conduct an extensive evaluation of potentially avoidable pediatric hospitalizations. The issue is of particular importance in light of the current emphasis on cost savings.
Regional and National Significance

The project has national significance because of the large number of potentially preventable hospitalizations each year. Since the research findings could have a major impact on the management of pediatric illnesses, this study also has clear implications for maternal and child health policy.

Scientific and Technical Merit

The current proposal has incorporated a number of revisions, and the pre-award commentary reflects the fourth review of the application. At the November 1996 review committee meeting, the application was deferred pending a site visit (April 1997); after the visit, a review committee team suggested additional changes to strengthen the revised proposal.

The project is designed to evaluate a fundamental question: How much of the current pediatric inpatient care for common childhood illnesses can be replaced with HNEPC? The investigators propose that the HNEPC intervention will be evaluated in four phases: (1) The preparation phase, for which funding has already been secured; (2) the research pilot phase, which would take place during the first 4 months of the proposed project and would serve to refine procedures and instruments in field situations; (3) the main study phase, in which the randomized clinical trial would take place, and (4) the data analysis phase. Primary outcomes of interest are the comparative costs of the two treatments, and the quality of care.

The researchers cite previous studies to support their belief that HNEPC can provide a low-cost, effective alternative to pediatric hospitalization. They report that a significant percentage of pediatric hospitalizations are (in retrospect) judged avoidable, that repeated pediatric hospitalization increases the likelihood of vulnerable child syndrome and other childhood developmental problems, and that home nursing has been shown to be relatively safe and effective for moderately severe illnesses.

The following issues were of concern to the committee: (1) The project staff’s lack of sufficient expertise and experience in clinical trials; (2) unclarified budget issues, specifically with respect to what costs would be paid by private insurers for the medical treatment, and what costs would be supported by the Maternal and Child Health Bureau for the research and evaluation component; and (3) the appropriateness of the “alternate days” design with respect to potential confounding when evaluating the efficacy of the proposed intervention.

Responding to the first and third points, the research team proposed a scientific advisory board consisting of specialists and experts in four main areas: Community and preventive medicine, nursing, biostatistics, and health services-economic decision analysis. Furthermore, two consultants would be added, a biostatistician with expertise in clinical trials, and a specialist in community and preventive medicine. The proposed scientific advisory board would provide an additional oversight mechanism to ensure that the research protocol is followed faithfully throughout the project period, especially in light of the uncertainty regarding third-party payment for home nursing care.

Responding to the second point (the alternate days design), the research team proposed an alternative design that addresses a concern expressed by a number of the reviewers. The new design would incorporate randomization by episode rather than by day. Proposed strengths of the new design include unbiased estimates of both the quality of the intervention and the communitywide costs. Furthermore, classification of the patient’s condition at presentation can be done by emergency department providers blinded to the patient’s control or intervention status. Although
some reduced power to detect effects can be expected for any given question, the preliminary estimates provided suggest a rather minimal loss, given the greater range of questions to be addressed.

Issues of financial responsibility for the proposed intervention were discussed by hospital administrators and financial officers, several of whom strongly indicated their commitment to seeing this project come to fruition. The investigators have been informed that the National Institute of Nursing Research has agreed to fund the proposal at a level of support in direct costs for 3 years, and would consider joint funding with the Maternal and Child Health Bureau. This is an important study in a priority area of maternal and child health; approval is recommended.
Role of Early Family Supports in Adult Self-Sufficiency

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University of North Carolina at Chapel Hill

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Project Number MCJ-370632
Project Period 6/1/96–5/31/00

Costs

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Year 2000 Objectives
8.2, 8.3

Study Design
Experimental

Time Design
Longitudinal

Care Emphasis
Interventional

Population Focus
Parents, Young Adults

Race/Ethnic Focus
African Americans

Summary

Statement of the Problem

This study addresses the long-term multigenerational outcomes of the Abecedarian Project, a randomized clinical trial of early childhood development intervention. This research represents the endpoint of a 21-year longitudinal study that began in the early infancy of the study subjects. The study seeks to address the problem of identifying the ecological, personal, and situational factors associated with outcomes for participants in young adulthood.

Further study of long-term outcomes from early intervention is also important from a practical point of view. Billions of dollars are allocated annually to improve the educational performance of low-income children. Adult outcomes from a previous intervention program, the Perry Preschool Project, suggested that every dollar spent on early childhood education resulted in an eventual savings of $8 because of increased employment and reduced crime. The Abecedarian Project, which provided similar but more intensive early educational treatment, affords a unique opportunity to learn whether the findings of the Perry Preschool Project can be replicated in another sample.

Research Questions or Hypotheses

The assessment of the long-term outcomes of the Abecedarian Project addresses a major scientific question: The malleability of intellectual/cognitive development given early environmental support and enrich-
The current followup study will examine the degree to which early educational treatment is reflected in different developmental trajectories and in the concurrent life adjustment of young adults. The investigators will examine the effect of early child care on the levels of educational attainment, self-sufficiency, and social adjustment in young adults and their parents. Specifically, the project will document whether earlier effects of care contribute to adult competence, and whether contextual and personal variables modify the effect and are related to the trajectory of development. Parental outcomes will also be examined among participants for whom the preschool intervention represented a significant family support: free child care.

**Study Design and Methods**

This is a prospective, longitudinal, randomized clinical trial. The Wechsler Adult Intelligence Scale–Revised will measure general intelligence. The Woodcock-Johnson Psycho-Educational Battery–Revised will measure reading and math achievement. The School Archival Records Search (SARS) will be used to abstract cumulative secondary school records. The SARS provides a framework for describing educational histories, including demographics, in-school and out-of-school referrals, negative comments, and disciplinary contacts.

The Parent of a Young Adult Interview (PAI) and the Young Adult Interview (YAI) will measure current educational status, attitudes toward educational experiences, living circumstances, and attitudes toward school. Complete histories of schools attended and diplomas and degrees earned will be obtained. The Scale of Independent Living, an instrument developed specifically for this study, will be used to summarize self-sufficiency in economic support, living arrangements, transportation, and medical care.

The Adult Nowicki-Strickland Internality-Externality Scale (ANS-IE) will assess locus of control. The Multi-Group Ethnic Identity Measure (MEIM) will measure three aspects of racial identity: Positive ethnic attitudes and sense of belonging, ethnic identity achievement, and ethnic behaviors and practices. Adapted from the Saranson’s Life Events Scale, the Taylor Life Events Inventory will be used with low-income families and modified to include events in the past year relevant to young adults.

**Population Description and Sampling Plan**

The original sample was first recruited between 1972 and 1977. All study participants had incomes within then-current Federal poverty guidelines, and 98 percent were African American. Infants with physical disabilities or syndromes associated with retardation were ineligible for inclusion. The original sample comprised a total of 111 children from 109 families. The current study will follow 105 young adults from 103 families. (The remaining subjects were omitted from the current sample because of death, seizure disorder, or refusal to participate.)

**Analysis Plan**

The analysis will test the primary hypotheses concerning the long-term correlates of early educational intervention and will evaluate interactions among individual, family, and community influences on development. The findings are relevant to priority areas involving the growth and development of minority children living in poverty and will provide important answers concerning ecological, personal, and situational factors associated with different developmental trajectories.
Pre-Award Evaluation

Originality and Importance

This application presents a clearly written, thorough, and comprehensive review of the literature. The study is grounded in an ecological framework that has guided other analyses to date. As the study subjects enter adulthood, important questions emerge. For example, what are the effects of the early childhood intervention on rates of substance abuse, employment, education, and the need for public assistance? These are important social policy questions, and this study can provide the necessary data and analysis.

Regional and National Significance

This proposed study has several strengths and it addresses an important topic. Interventions that assist minority children in maximizing the benefits of education and making successful transitions to adulthood may have widespread national and regional importance.

Scientific and Technical Merit

The investigators make a clear distinction between the data that have been collected previously and the data to be collected in the proposed study. The proposal includes previously measured child and parent variables, including mother's IQ, attitudes, and locus of control, and the child's cognitive and social development in infancy and periodically thereafter. In addition, the psychometric properties of the instruments to be used are presented, as are the availability of normative data for African-American children and young adults. Another strength of the study is that data will be collected at age 21 from instruments that are comparable to those used previously in the Abecedarian study.

The researchers have been extremely successful in holding their sample over time with very low attrition. Of the 111 original subjects, the researchers hope to include 105 in the 21-year followup. This level of retention is particularly impressive since the young adults must invest up to 8 hours in providing data and information for the study.

The proposed study has a number of weaknesses. Although the investigators provide a framework for their proposed work, the conceptual link between early education and adult competence is not well-developed. The effect of the intervention on the parents of the children who received the intervention is particularly questionable.

The list of variables to be obtained for the young adults is not well-focused. There are too many instruments used in the study for the few degrees of freedom in the sample. The list of instruments is not effectively integrated into the conceptual framework, and it is at times unclear what construct the instrument is supposed to measure. The reader has to go back to the conceptual framework or analysis plan to know where the instruments fit into the conceptual model. Some of the new measures that the investigators propose to collect do not fit the conceptual model, or at least no rationale is provided as to how they fit. While there is a great deal of interest in studying racial/ethnic identification, the investigators appear to be stretching their conceptual framework. The life events scales duplicate some of the data obtained in other instruments.

Some of the study's approaches to data analysis appear to be in reverse order. The investigators plan to do the multivariate analysis first, and then conduct the univariate analysis. The univariate analysis should be done first.

Data will be obtained from the young adults...
and parents over a 3-year period. The costs associated with the data collection are extremely high for the proposed work. Similarly, in year 4 no data are to be collected, yet the budget is comparable to years 1–3. This is an extremely experienced research team, who are fully capable of collecting, analyzing, and interpreting their data. The requested consultants are not needed and should be deleted from the budget.

The research questions addressed by the application are extremely important. The application is well-written and technically sound. However, there are far too many variables that are not conceptually linked. Nevertheless, the recommendation is for approval, with the condition that prior to funding the investigators submit a revised plan that includes

1. A reduced set of variables that address the most important potential effects of the early childhood intervention;
2. A clear conceptual link between this set of variables and the early intervention; and
3. A reduced budget that reflects a more parsimonious set of variables and excludes all consultant costs.
Psychosocial Sequelae of Bronchopulmonary Dysplasia and Very Low Birthweight-Phase Two

Grantee
Case Western Reserve University

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Project Number  MCJ-390715
Project Period  2/1/97–1/31/2001

Costs

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<tr>
<td>Year 4</td>
<td>196,186</td>
<td>32,250</td>
<td>228,436</td>
</tr>
<tr>
<td>Year 5</td>
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</tbody>
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Year 2000 Objectives
6.3, 6.13, 6.14,17.2,17.15, 22.4, 6.5

Study Design
Quasi-experimental

Time Design
Longitudinal

Care Emphasis
Noninterventional

Population Focus
School Age Children, Parents

Race/ Ethnic Focus
African Americans

Summary

Statement of the Problem

Bronchopulmonary dysplasia (BPD), a chronic lung disease of prematurity, currently occurs in 25 to 40 percent of very-low-birthweight (VLBW) infants and has been found to be significantly related to poorer developmental outcome in VLBW cohorts. The first waves of postsurfactant survivors are now approaching school age, with little known about their long-term pulmonary outcomes, growth, or functional abilities. Further, there is little available data on the behavioral, psychosocial, and family outcomes of VLBW cohorts in general, and no data in which prospectively recruited cohorts of VLBW and term comparison groups have been longitudinally assessed to identify the processes by which outcomes might be affected.

Delineating the specific relationships between early medical conditions (such as BPD) and (1) other complications of preterm birth and (2) child outcomes may lead to early identification of those VLBW children at highest risk for learning and behavior problems; it may also elucidate biological and psychological mechanisms related to the negative sequelae of VLBW birth.

Research Questions or Hypotheses

Four study hypotheses are posed:
1. At 7 1/2 years of age, children with a history of BPD and VLBW are expected to continue to exhibit impaired functioning, compared with VLBW children without BPD and term children of similar age,
race, sex, and socioeconomic status (SES), when assessed on measures of physical health and growth, lung function, cognition, school achievement, language, behavior; and specific neuropsychological abilities.

2. Parents of children age 7 1/2 who had BPD are expected to experience more symptoms of psychological distress and more stress, and to have less optimal interactions than parents of children without BPD and parents of term children.

3. After other neurological, medical, and SES risk factors have been taken into consideration, BPD is expected to account for independent variance in overall cognitive, motor, and neuropsychological outcomes in children.

4. BPD and VLBW are expected to have direct effects on children’s school achievement, and indirect effects through their impact on both earlier and concurrent maternal distress and mother-child interactions.

The proposed research will investigate school-age functional abilities, with a particular focus on the influence of BPD (relative to other risk factors) on pulmonary, cognitive, language, neuropsychological, and behavioral/emotional outcomes.

**Study Design and Methods**

Standardized measures of child outcomes will be administered, teacher and parental report of child behaviors will be obtained, and parental self-report of psychological and parenting distress, coping mechanisms, and social supports will be provided. Videotaped observations of maternal-child interactions will also be made.

Study measures to be collected include a medical history focusing on lung, cardiac, kidney, and neurological problems; vision examination; physical assessment; hearing screening; conversational language sample; and measurements of weight, height, and lung function. The Wechsler Intelligence Scale for Children (WISC III), Woodcock-Johnson Tests of Achievement, Continuous Performance Test of Attentional Processes, Bruininks-Oseretsky Test of Motor Proficiency, Clinical Evaluation of Language Fundamentals, and the Children’s Pictorial Depression Scale will be used.

Teachers of study children will be asked to complete the Adaptive Language Inventory and the Connors Teacher Rating Scale. Parents will be asked to complete the Child Behavior Checklist, the Parenting Stress Index, COPE, the Brief Symptom Inventory, the Multidimensional Scale of Perceived Social Support, and the Family Inventory of Life Events and Changes.

**Population Description and Sampling Plan**

The study sample will comprise 302 white and African-American children ages 7 1/2 who were followed prospectively from birth to age 3 in two separately funded longitudinal studies of the medical and psychosocial correlates of BPD and VLBW. Of the 302 children, 110 were VLBW at birth with subsequent BPD, 80 were VLBW at birth without BPD, and 112 were healthy term infants. The groups do not differ in age, race, sex, SES, or parental education/marital status.

Ninety children will be assessed each year for the first 3 years of the study, and 32 children will be assessed during year 4.

**Analysis Plan**

Descriptive statistics, multiple analysis of variance (MANOVA) and multiple analysis of covariance (MANCOVA), and hierarchical multiple regression will be used to assess group differences and the relative effects
of BPD, VLBW, and other risk factors on outcome. To assess change over time and predictive models of infant risk, data sets from the two prior longitudinal studies will be merged with the outcome data from this study, and hierarchical linear or structural equation models will be applied.

Pre-Award Evaluation

Originality and Importance

This is the second phase of a continuation study of bronchopulmonary dysplasia (BPD), a chronic lung disease affecting an estimated 7,000 infants each year. Very low birthweight (VLBW) infants with BPD constitute approximately 25 to 40 percent of VLBW survivors, so this is an important group to study longitudinally. The continuation phase of this study provides the opportunity to follow a group of BPD and VLBW infants into the early years of school. Following VLBW infants through the early elementary school years should provide information that will increase our understanding of the developmental outcomes of VLBW children, including those with BPD.

Regional and National Significance

This important study has both regional and national significance. The research to date has been competently executed and has resulted in numerous quality publications.

Scientific and Technical Merit

This application is a revision of a proposal initially reviewed in June 1996. Although the previous review panel pointed out the application’s numerous strengths, several important weaknesses were also noted. The researchers have revised the proposal to address each concern raised by the review panel. In general, the investigators have been very responsive to comments in the initial review. Concern was expressed that the small number of cocaine-exposed infants in the sample would preclude meaningful analyses. This group was dropped from the revised application.

The investigators argue that long-term developmental outcomes for this group are largely unknown. They hypothesize that children who had BPD in infancy will exhibit, by the time they reach school age, a lag in cognitive and behavioral competence relative to their VLBW and term peers. Understanding the long-term outcomes of infants with BPD may partially explain the heterogeneous outcomes of VLBW infants.

All parents whose children were enrolled in the prior studies in 1989–91 (except for the small group of cocaine-exposed infants) would be recontacted and asked to make a followup visit to the researchers’ laboratory. To date, study data have been collected on the infants at 1, 8, 12, 24, and 36 months of age. The infants who participated in the first phase of the study became eligible for the 7.5 year followup beginning in January 1997.

The review panel noted that clear information on past and anticipated attrition was not presented in the original application. The revision contains more detailed information on attrition. Power analyses including attrition estimates were provided, creating confidence that a sufficient sample of children will remain for the 7.5 year followup to support the desired data analyses. As requested, the researchers also provided a definition for the classification of children as having mental retardation. In addition, issues relating to subject replacement have been clarified (i.e., no subjects are to be replaced).

One of the review panel’s more substantial concerns relates to whether the amount of variance in BPD-related child outcomes is sufficient to warrant continuation of the longitudinal data collection.
Reviewers also noted that many of the differences between BPD and VLBW infants in the initial study disappeared after socioeconomic status, parenting, and neonatal risk factors were controlled. To address these concerns, the investigators argued that their results to date are clinically significant and thus important, regardless of the amount of variance accounted for by BPD. After other factors are accounted for, BPD was found to be responsible for a 10-point decrement in the third year's Psychomotor Development Index on the Bayley Motor Development Scale. This is a .5 standard deviation on this measure, and the investigators argue that this is clinically significant. By 3 years of age, the effects of BPD on cognitive development had disappeared, but the investigators have indicated their interest in looking for “sleeper” effects in cognitive development, which may emerge as the children progress in school.

The review panel requested additional information on the meaning of study findings concerning lower performance by BPD infants at 3 years on receptive, but not on expressive, language skills. In the revised application, the investigators speculated that the receptive language deficit may be due to undetected hearing impairments in the BPD infants. A hearing screening was not included in the initial data collection protocol. Other possible explanations presented by the investigators include poor attending to the receptive test and the possible presence of actual receptive-expressive language differences resulting from neuropsychological problems.

As requested by the review panel, the investigators provided additional information in the revised application concerning factors they believe will mediate and moderate the effects of BPD on children. They provide examples of how these processes may operate, along with preliminary STM analyses. The researchers also cite recent papers that have addressed these issues.

The former review team noted that the data protocol was extremely extensive; the approach seemed to be one of trying to measure as many things as possible, to “cast a wide net” in order to detect possible group differences. This approach lacked focus and made the research extremely expensive. The panel suggested streamlining the data collection protocol substantially, focusing on those outcomes considered critical in the researchers' previous work. The researchers have been only partially successful in this regard. Several measures have been dropped, including the Tactual Performance Test, the Marching Test, the Category Test, the Narrative Skills Task Skillbook, the Goldman-Fristoe Test of Articulation, and the Oral and Speech Motor Control Protocol. Even so, the data to be collected are still very extensive, without a compelling rationale for including or excluding measures. Although the budget has been reduced, the data collection remains an extremely expensive effort, in part because of the large number of measures to be collected.

The study includes two primary racial/ethnic groups, Euro-Americans and African-Americans. Concern was expressed during the past review that study measures were not selected based on their appropriateness for these groups of families. In the revision, each measure has been justified (to the extent possible), based on its use with African-American children and families. In addition, preliminary data analyses have been conducted, examining racial/ethnic differences in the processes underlying study outcomes.

In summary, the investigators and supporting staff are well qualified and have sufficient experience to conduct the proposed study. The proposal has been approved by the Institutional Review Board. Human subjects protections appear to be adequate. Continuation of the research is recommended, with a reduction in the budget.
Early Cortisol Replacement to Prevent BPD: Pilot Study

Summary

Statement of the Problem

Bronchopulmonary dysplasia (BPD), chronic lung disease following neonatal lung injury, affects a majority of extremely low birthweight (ELBW) babies (<1,000 grams birthweight) and is a leading cause of morbidity and mortality in this population. Oxygen toxicity and barotrauma have been postulated as etiologic factors; increasing evidence also implicates inflammation in its pathogenesis. Corticosteroids are essential for the resolution of inflammation and have a myriad of other effects on lung development, structure, and function. Both basal cortisol concentrations during the first week of life and cortisol secretion in response to adrenocorticotropic hormone (ACTH) stimulation at the end of the first week of life are significantly lower in babies who subsequently develop BPD than in those who recover. ELBW babies also have been reported to show symptoms consistent with adrenal insufficiency early in life, responsive to hydrocortisone (HC) supplementation. Early, high-dose steroid therapy in the first 2 weeks of life has been reported to decrease the incidence of BPD; however, these very large doses also produce unwanted side effects and may not be necessary.

Research Questions or Hypotheses

This pilot study is designed to estimate the benefits and safety of supplementation with physiologic doses of HC during the first 12 days of life to decrease the incidence of subsequent BPD. The results of
this pilot study will be tested to calculate an appropriate sample size for a future multicenter trial. The secondary hypothesis is that this therapy will improve physiologic stability during the treatment period.

**Study Design and Methods**

The study design is a randomized, placebo-controlled, single-center trial. The relationship of clinical outcome to the adrenal axis will be assessed for 17-OH progesterone, II-desoxycortisol, dehydroepiandrosterone, and cortisol, through analysis of blood samples obtained at days 1 and 6, and for ACTH on day 6. After the infant’s completion of HC therapy, cortisol response to ACTH will be tested. The relationship of these factors to inflammation will be assessed by analyzing tracheal lavage specimens for markers of lung inflammation (interleukins 1ß, 6, and 8; elastase; and inflammatory cells) and by measuring cell adhesion molecules (CD18 and CD62L) on peripheral blood neutrophils with flow cytometry.

**Population Description and Sampling Plan**

Forty intubated newborns between 500 and 999 grams birthweight will be enrolled before 48 hours of life and treated with HC or placebo for 12 days. Primary measures of efficacy will be survival without oxygen dependence at 28 days of life and 36 weeks postconception. Secondary clinical variables will be indicators of adrenal insufficiency during the therapy period.

**Analysis Plan**

Evaluating acute and long-term clinical outcome measures in conjunction with laboratory measures of adrenal hormones and inflammation will allow a preliminary assessment of both the clinical efficacy of early cortisol replacement therapy and the relationship between that level of efficacy and one pathophysiologic mechanism: inflammation. This pilot study would thus provide a basis for both multicenter clinical trials of efficacy and further elucidation of the pathophysiology of BPD.

**Pre-Award Evaluation**

**Originality and Importance**

Bronchopulmonary dysplasia (BPD) affects about 30 percent of all babies weighing less than 1,500 grams at birth and is a leading cause of morbidity and mortality in this population. Oxygen toxicity and barotrauma have been postulated as etiologic factors; increasing evidence also points to inflammation as a factor.

Corticosteroids are essential for reducing inflammation. Cortisol secretion in response to ACTH stimulation at the end of the first week of life is significantly lower in babies who subsequently develop BPD than in those who recover. It also has been reported that immature babies with symptoms consistent with adrenal insufficiency are responsive to hydrocortisone supplementation.

**Regional and National Significance**

This study will help determine whether supplementation with physiologic doses of hydrocortisone (HC) during the first 12 days of life will decrease the incidence of subsequent BPD by dampening an exaggerated inflammatory response. The study will also provide information on whether this therapy will improve physiologic stability during the treatment period.

The study will investigate the effect of cortisol replacement therapy on adrenal hormone concen-
toration and the ability of the adrenal gland to respond to ACTH. The effect of replacement therapy on markers of inflammation in lung lavage fluid and peripheral blood leukocytes will also be determined. Therefore, this study clearly is of regional and national significance.

**Scientific and Technical Merit**

This submission is a revision of a previously disapproved application. The hypotheses posed by this double-blinded, randomized, placebo-controlled trial are carefully stated and testable. An extensive literature review is presented in support of the hypotheses. Preliminary work done by the investigators supports the proposal and demonstrates their expertise and capabilities to perform the work as proposed.

The magnitude of the HC dose will be modified based on a pilot study currently underway to evaluate the pharmacokinetics of exogenous HC. The dose will be given for 9 days and will be tapered for 3 days at half the original dose. Adverse effects—in particular, disseminated candidal infections—are anticipated to occur after 12 days, but other factors may affect this, and the need for long therapy cannot be examined in this study.

The description of the laboratory studies (involving adrenal hormone analysis, tracheal aspirate measures, and cell surface adhesion molecules) appears adequate. The proposal addresses quality control methods for consistency of treatments, data collection, and comparability of lab tests.

Exclusion and inclusion criteria are addressed, but questions remain. Of interest is the occurrence of congenital sepsis in patients and their need to withdraw from HC therapy. What is the likelihood of this happening, and will sepsis rates be monitored? The exclusion of these patients will surely affect the sample size of a later trial.

The application does not clearly explain the factors that are not known but must be known to plan the major trial (e.g., the effect of mortality censoring on the ability to assess the benefits of cortisol, and the need to withdraw from study medications). Power analysis is not an issue here, but monitoring selected outcomes and situations to determine the feasibility of a future study is.

A sample of 40 babies is quite big for a pilot study. The proposed data analyses seem appropriate, but performing them on all 40 infants may be overkill.

The principal investigator and coinvestigator will remain blinded to the study. How will this be accomplished? Who will be responsible for breaking randomization codes, and who will make recommendations to continue/discontinue/modify the study?

No interim analyses will be performed, and there is not much information about the nature of the expected attrition. Will the attrition be in the form of refusal to participate or withdrawal from the study?

Members of this research team have published numerous articles on this topic and are well-qualified to conduct the proposed research. The budget for the statistical analysis seems very generous in light of the sample size.

The research questions posed by this study are important. The application document is well-written and, for the most part, technically sound. The recommendation is for approval, with the condition that the principal investigator clarify whether all eligible babies will be enrolled sequentially, at intubation, at 12–48 hours, or at other times. A strong case can be made for including all 500–999-gram babies, since mechanical ventilation occurs early or is not always used for BPD (BPD as defined equals 28 days of oxygen use). As a second condition for approval, the principal investigator must provide explicit criteria for the following:
1. Under what conditions would the investigators feel ethically bound to stop the trial?

2. Because the babies being studied are extremely sick, it is likely that there will be tremendous pressure to break codes in the case of certain infants. What will be the criteria for individual babies exiting the trial?

3. Data collection forms should be provided.

4. Handling of certain variables (sex, severity of illness, use of antenatal steroids, presence of maternal chorioamnionitis, etc.) must be made explicit for the analytic phase.