

ANNUAL REPORT,
OF
PROGRAM ACTIVITIES
NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT,
Fiscal Year 1982

National Institute of Child Health and Human Development

TABLE OF CONTENTS

	Page
<u>Office of the Director</u>	1
 <u>Center for Population Research</u>	
Office of the Director	5
Contraceptive Development Branch	14
Contraceptive Evaluation Branch	65
Social and Behavioral Sciences Branch	83
Reproductive Sciences Branch	153
 <u>Center for Research for Mothers and Children</u>	
Office of the Director	169
Clinical Nutrition and Early Development Branch	171
Mental Retardation and Developmental Disabilities Branch	217
Human Learning and Behavior Branch	233
 <u>Epidemiology and Biometry Research Program</u>	
Office of the Director	243
Biometry Branch	255
Epidemiology Branch	279
Computer Sciences Section	289
 <u>Intramural Research Program</u>	
Laboratory of Developmental Neurobiology	291
Laboratory of Molecular Genetics	319
Child and Family Research Branch	335
Pregnancy Research Branch	351
Developmental Pharmacology Branch	377
Neonatal and Pediatric Medicine Branch	391
Endocrinology and Reproduction Research Branch	403
Developmental Endocrinology Branch	429

NICHD ANNUAL REPORT

October 1, 1981 through September 30, 1982

OFFICE OF THE DIRECTOR

The National Institute of Child Health and Human Development has broad responsibilities for research on problems of growth and development. In the United States about two-thirds of all deaths of newborns are associated with low birthweight or prematurity, and the infant death rate is higher than that of 13 other countries. Each year, hospital costs for intensive care of premature infants exceed \$1.5 billion. Of every 1,000 live births, 70 infants enter the world with mental or physical defects; the causes of 65 to 70 percent of these defects remain unknown. Adolescent pregnancy is an issue of continuing concern. Although declines in the adolescent birth rate have recently been recorded, the rates are still high among very young adolescents, who are also most likely to have complications of child-bearing and childrearing. Many pregnancies are unwanted, and, conversely, many couples who want children are unable to have them.

To approach solutions to these and similar health issues, the NICHD has based its programs on the concept that adult health and well-being are determined in part by episodes early in life, that physical and mental change is continuous throughout life, and that reproductive processes and the management of fertility are of major concern not only to the individual but to society. The Institute's goal is to assure the means of improving health and well-being through advances in knowledge of human reproduction, growth, development, and maturation. Nationally and within its own facilities, the NICHD conducts and administers a program of clinical and fundamental research and research training, encourages and assists in the transfer of findings to practice, and disseminates information about research advances in child health and human development to scientists, health practitioners, and the public.

Organizationally, the Institute accomplishes its research effort through the programs of the Center for Research for Mothers and Children (CRMC), the Center for Population Research (CPR), the Intramural Research Program (IRP), and the Epidemiology and Biometry Research Program (EBRP). The summaries and/or project descriptions of research accomplishments within these programs constitute the report of the Institute for this fiscal year.

Significant among the reports of accomplishment in a great variety of research areas are the developments occurring with synthetic copies of natural peptide hormones, specifically luteinizing hormone-releasing hormone (LHRH). LHRH is now in transition between basic research and clinical application. A few reports have been received of successful clinical use. For example, the first cure of a rare type of male infertility using LHRH was recently reported, and LHRH has been used on a limited basis to treat certain forms of female infertility. Institute intramural scientists have also used LHRH in the first successful treatment of precocious puberty, a condition in which affected infants and children prematurely begin the process of puberty with the accompanying physical changes.

In a different application, there is evidence that LHRH has the potential for becoming the first successful contraceptive drug for men and a safe once-a-month birth control pill for women. Very limited clinical trials using the drug for these purposes have been started; early results are promising, but much more testing and development are necessary before LHRH will be available as a contraceptive agent.

Fiscal year 1982 has been a year of transition in the leadership of the NICHD. The position of Director was vacated in the summer of 1981 and Dr. Betty H. Pickett, Deputy Director, filled the position as Acting Director until July 1, 1982.

Dr. Pickett's adept use of management skills and intimate knowledge of grants

administration assured a stable and confident handling of Institute affairs during this period.

Dr. Sumner J. Yaffe became Director of the CRMC at the start of the fiscal year. His contributions toward unifying procedures and resources and sharpening the focus of research objectives already provide indication of improved productivity in the important programs of the Center.

Finally, July 1, 1982, Dr. Mortimer B. Lipsett was appointed NICHD Director by the new NIH Director, Dr. James B. Wyngaarden. Dr. Lipsett is an internationally recognized expert in development endocrinology who has served in research and management roles with the NIH for 23 years. Since 1976, as Clinical Center Director, he had managed the largest hospital in the world devoted solely to medical research. He was associated with the NICHD from 1970 to 1974 as Associate Scientific Director.

Reports of effort and achievement are recorded in the pages that follow. Staff and management of the NICHD are optimistic for improved successes in the future.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Center for Population Research
Office of the Director

INTRODUCTION

The Institute's Center for Population Research (CPR) continued to fulfill its responsibility for the primary Federal effort in population research. Significant progress has resulted again this year from CPR's support of research in the population sciences through grants and contracts for:

- Fundamental biomedical research in the reproductive sciences relevant to problems of human fertility and infertility.
- The development of safe and efficacious methods for fertility regulation.
- The evaluation of the medical effects and efficacy of contraceptive methods currently in use.
- Social and behavioral sciences research on the causes and consequences of population structure and change.

The Center is directed by Dr. Philip Corfman and by Mr. Arthur Campbell, Deputy Director, and is organized into four branches corresponding to the above objectives. The Reproductive Sciences Branch is headed by Dr. William Sadler; the newly appointed Chief of the Contraceptive Evaluation Branch is Dr. Jeffrey Perlman; the Contraceptive Development Branch is headed by Dr. Gabriel Bialy; and the Chief of the Social and Behavioral Sciences Branch is Dr. Wendy Baldwin.

The following provides a brief description of CPR, NICHD's programs and lists some of the recent findings and achievements in these areas of population research supported by the Institute.

REPRODUCTIVE SCIENCES

Research in the reproductive sciences on fertility and infertility is concerned with the reproductive process involved in the fertility of men, women, and animals with reproductive processes similar to those in human beings. Studies on fertility and infertility are subsumed under the four major disciplines which comprise the reproductive sciences: (1) reproductive endocrinology; (2) reproductive biology; (3) reproductive medicine; and (4) reproductive chemistry. Reproductive endocrinology includes the secretion, action, and metabolism of the reproductive hormones and the endocrine glands which secrete them. Reproductive biology includes the reproductive processes and events such as oocyte maturation, sperm production, ovulation, sperm maturation, sperm capacitation, gamete transport, fertilization, early embryonic development, implantation, reproductive behavior, and nutrition in animals. Reproductive medicine includes human nutrition, human infertility, human reproductive diseases and disorders, andrology,

and clinical studies of human reproduction. Reproductive chemistry includes synthesis of reproductive peptides and steroids, isolation and purification of substances involved in reproduction; and chemical modification of substances involved in reproduction for increased efficacy and diminution of undesirable side effects.

Recent Research Results in the Reproductive Sciences

1. Studies of various steroidogenic enzyme activities related to testicular testosterone production have provided evidence that the structural components of the testes (the Leydig cells and the seminiferous tubules) appear to contain two forms of an enzyme (17-ketosteroid reductase) which catalyzes the final step in the biosynthesis of testosterone. Increased knowledge of the various enzymes involved in testosterone biosynthesis is important for the understanding of normal testicular function and for developing possible new approaches to the alleviation of male infertility.
2. Evidence has been obtained for the localization of secretions of the oviduct within oviductal tissue (ampulla, the ampullar--isthmic junction and the isthmus) and it suggests that secretory granules within all regions of the oviduct do not contain similar components. These findings indicate that specializations within regions of the oviduct may be responsible for specific functions of the oviduct in the critical events of fertilization and embryo development.
3. Progress has been made in characterizing the biochemical and physical properties of the mechanisms of action of the luteinizing hormones. The first studies of free biologically active human chorionic gonadotropin (hCG) within its target cell have been reported. In producing its effects on its target cell, gonadotropin appears to be internalized into the cell and this process is accompanied by marked alteration of its carbohydrate component. After internalization, hCG remains biologically active for unexpectedly prolonged periods. This new knowledge regarding the mechanisms of action of the gonadotropic hormones increases our understanding of reproductive processes.
4. In a recent study of the relative nuclear content of receptors with estrogen attached (occupied) and receptors without estrogen attached (unoccupied), progesterone caused a preferential and accelerated loss of occupied estrogen receptor complexes. It was found that the releasing factor activity is inhibited by types of inhibitors that affect phosphatase enzymes. The results demonstrate for the first time a unique progesterone - induced releasing activity which acts selectively on the occupied forms of the estrogen receptor. These findings provide a significant advance in understanding the mechanism of action of steroid hormones.
5. The role of the ovarian peptide, folliculostatin, in the control of follicle stimulating hormone (FSH) secretion has been further defined. It has recently been shown that an antagonist to gonadotropin releasing hormone (GnRH) in ovariectomized rats suppresses serum luteinizing hormone (LH) by 90 percent while serum FSH is decreased by only 60 percent. This suggests that while LH secretion is highly coupled to GnRH, a considerable fraction of FSH secretion is independent of GnRH.

6. Significant findings resulted from a study in which a luteinizing hormone releasing hormone (LHRH) agonist and an antagonist were tested for their ability to inhibit progesterone secretion by cultured human granulosa cells. When granulosa cells were harvested from large follicles during the late follicular phase and cultured with an LHRH agonist at relatively low concentrations, steroid production by the granulosa cells was inhibited. An LHRH antagonist had no marked effect on progesterone production, but it negated the inhibitory effect of the agonist. These results indicate that LHRH-like substances can directly influence ovarian cell function in the human and that some LHRH agonists may act directly on the ovary.

7. Information concerning two frequent causes of amenorrhea in infertile women, polycystic ovarian syndrome and premature ovarian failure, has been obtained from studies of new methods of ovulation induction. Preliminary data indicate that altered metabolisms or excretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) may exist in some individuals with premature ovarian failure and suggest that abnormal species of FSH and LH may play a role in the development of this disease. Studies on polycystic ovarian disease suggest that the inhibitory effects of endogenous opioid peptides on LHRH release are functionally reduced.

8. Significant progress has been made in establishing a suitable animal model for studying the role of small microorganisms known as Chlamydia in relation to pelvic inflammatory disease (PID) and infertility. The ability to experimentally infect the uterus and Fallopian tubes of guinea pigs has been confirmed. An important new finding is that the apparent resolution of the acute inflammatory process (within three weeks after inoculation) is followed by an accumulation of watery fluid in the distended uterine tubes of most of the animals. This condition, called hydrosalpinx, is similar to that observed in the human and is associated with infertility that appears to be due to a mechanical blockage of the ends of the Fallopian tubes. The experimental model that has been developed will enable continued advances in our understanding of the role of Chlamydia infection and hydrosalpinx in infertility.

9. The first successful cure of an infertile man by administration of synthetic luteinizing hormone releasing hormone (LHRH) has recently been confirmed by the birth of a child. Administration of synthetic LHRH to men who have a deficiency of their own endogenous LHRH results in the synthesis and release of gonadotropins which, in turn, stimulate the production of sperm by the testes. A major breakthrough for the successful therapeutic use of this hormone was the discovery of the necessity for its intermittent or pulsatile administration. A portable mini-infusion pump was adapted for the pulsatile delivery of LHRH which had to be administered over a period of many weeks.

CONTRACEPTIVE DEVELOPMENT

Research activities included in contraceptive development are: (1) synthesis and biological evaluation of promising new compounds that may affect reproductive processes in the male or female; (2) the development of technology for improved administration of contraceptive drugs; (3) the development of improved vaginal and uterine contraceptives based on chemical or physical methods; (4) clinical trials of sex steroids and peptides for suppression of sperm production and the

consequent development of chemical contraceptives for men; (5) clinical and toxicological evaluation of long-acting progestin as a female contraceptive; (6) laboratory studies and clinical trials to develop and evaluate antifertility methods based on periodic abstinence; and (7) studies required to clarify mechanisms of action of specific contraceptive drugs.

Recent Research Results in Contraceptive Development

1. Important advances have occurred regarding the synthesis and testing of luteinizing hormone releasing hormone (LHRH) antagonists as antioviulatory agents. These efforts have resulted in the development of analogs that are active in blocking ovulation in the rat at subcutaneous dose levels below one microgram. Concomitant is the new observation of oral activity at modest dose levels (two milligrams) in the rat. As potent gonadotropin inhibitors, these LHRH antagonists also have the potential of acting as antispermatogenic agents.

2. The biological testing facility continues to assess some four hundred compounds annually for antifertility and classical endocrine activities. In addition to the evaluation of long-acting drugs for the purpose of female fertility regulation, the facility has been testing some of these drugs in the male as potential antifertility agents. Considerable inhibition of testes function has been observed with some of the long-acting progestins. Employing several different formulations of new esters, more sustained blood levels of testosterone have been observed than those achieved with testosterone enanthate.

3. Further progress is being made in the development of biodegradable drug delivery systems. As result of the successful Phase I clinical evaluation of the Capronor tubular capsule implant, a chronic toxicological evaluation is being implemented which will support a Phase II clinical study for safety and effectiveness. In addition, since injectable microcapsules of polylactide containing levonorgestrol have shown in animal studies to be worthy of further development, they will also proceed to chronic toxicology evaluation.

4. Preliminary data from the Phase III clinical trial of a polyurethane sponge diaphragm show that in comparison to the currently available diaphragm, there are no significant differences in the performance rates for the two methods. The sponge users seem highly enthusiastic about this device and it is anticipated that contraceptive sponges may be on the market soon for general use.

5. Findings from an ongoing preclinical evaluation of a new spermicidal contraceptive indicate that besides having greater spermicidal potency than presently available surfactant materials, the new compound may have certain unique properties. It appears to bind to the sperm, enter cervical mucus more readily, and causes disruption of the sperm membrane. Studies in monkeys indicate that it may remain active for as long as 12 hours, whereas most of the presently available spermicidal formulations are only active for 20 minutes to one hour.

6. Ongoing clinical studies with both men and women involving three different luteinizing hormone releasing hormone (LHRH) agonists are providing useful information regarding the clinical pharmacology of these drugs and their possible use for contraception. In female volunteers, results of administration of agonists during early luteal phase and mid luteal phase indicate that at present

the luteolytic approach does not appear to be feasible. Short term administration (one to two days) of agonists during early follicular phase has resulted in delayed ovulation and prolongation of the cycle, while late follicular phase administration appears to have little effect. Studies on the use of agonists in male volunteers indicate that doses of the agonists greater than 50 micrograms will be required to achieve effective suppression of spermatogenesis and that testosterone enanthate will have to be given to maintain normal libido.

CONTRACEPTIVE EVALUATION

Research on contraceptive evaluation includes the following: (1) Studies of steroid contraceptives to determine their effects on cancer, heart disease, hypertension, thromboembolic disease, metabolic, nutritional, and immunologic disorders. Also included are studies of the role of the immune system in mediating adverse effects of oral contraceptives and evaluation of individual variation in pharmacologic response to contraceptive steroids. (2) Studies of intrauterine devices to determine their effects on the occurrence of serious gynecologic and obstetric disorders such as pelvic inflammatory disease, vaginal hemorrhage, uterine perforation, ectopic pregnancy, fetal loss, abruptio placenta, placenta previa, and infertility, (3) Studies of the medical sequelae of male and female sterilization. (4) Studies of the effects of induced abortion on subsequent reproductive function, such as the occurrence of spontaneous abortion, prematurity, infertility, etc. (5) Studies on the use-effectiveness of inadequately evaluated methods, such as the diaphragm and condom.

Recent Research Results in Contraceptive Evaluation

1. Two case-control studies have found that women who have taken oral contraceptives over a long period of time are not at an increased risk of developing malignant melanoma of the skin. Previous studies that did not control for amount of sunlight exposure had given varying results.
2. A case-control study on pituitary adenoma in oral contraceptive users indicates that there is no correlation between the occurrence of pituitary adenomas and previous pill use. It appears, rather, that pituitary adenomas are being diagnosed in increasing numbers of women with secondary amenorrhea.
3. Preliminary analyses of data from a large ongoing study to evaluate the relationship between oral contraceptive use and the occurrence of breast, endometrial, and ovarian cancer provide no support for earlier reports that oral contraceptive use increases the risk of cancer. Furthermore, the data indicate that pill use seems to decrease the risk of endometrial and ovarian cancer.
4. The results of a large case-control study on the risk of diabetes in current and past users of oral contraceptives indicate that it now seems unlikely that use of contraceptive steroids will be statistically associated with the overall increase in the risk of diabetes mellitus among all users.
5. A study to determine whether there is a relationship between vasectomy and the extent of coronary artery arteriosclerosis in man, showed that the vasectomized men did not have a higher degree of coronary artery occlusion than their age-matched controls.

SOCIAL AND BEHAVIORAL SCIENCES

Research in the social and behavioral sciences is concerned with the factors governing variations in the growth, distribution, and characteristics of people and the impact of population changes on the health and well-being of individuals, families, and society as a whole. This research includes two major categories:

(a) Studies of the causes of population change, including factors affecting the three components of population change: fertility, mortality, and migration. Research has emphasized factors affecting fertility, since this has been the largest and most variable component of population change in the United States. Research on the causes of variations in fertility is concerned primarily with social, economic, and psychological determinants. Also included are such topics as choice of methods of fertility control, attitudes toward such methods, the effectiveness with which methods are commonly used, the number of children wanted and expected, changes in family structure and function, the desired timing of childbearing and the incidence of unwanted childbearing. Research on the causes of migration deals with factors affecting trends in internal migration, such as the movements between metropolitan and non-metropolitan areas, and immigration. Research in mortality includes studies of mortality differences between various social and economic groups and of social and economic factors affecting trends in mortality.

(b) Studies of the consequences of population change, including research on the personal, familial, and social consequences of changes and differentials in the components of population change (fertility, mortality, and migration) and the resulting characteristics and distribution of the population. Emphasis has been placed on the consequences of childbearing patterns for individuals, families, and society; for example, studies of the effects of maternal age, birth spacing, and birth order on the psychosocial development of the child, the economic well-being of the parents, the participation of women in the labor force and the stability of the family unit. Special attention is given to the consequences of teenage childbearing for mother and child. Research on the consequences of migration include the social and economic impact of large movements of people into or out of specific areas. Studies of the consequences of mortality include the impact of the size of specific age groups and the effects of family composition. Research on the consequences of population change also include studies of the social, economic, and other impacts of varying rates of population growth.

Recent Research Results in the Social and Behavioral Sciences

1. Studies of the demographic dynamics contributing to the change in family and household structure have provided significant insights. The percent of the population that will marry at least once is rising, although young adults seem to be postponing the age of marriage. While divorce rates are increasing rapidly they are not rising as fast as generally thought, and the rate of remarriage for those who have divorced is also rising. One study reports that about 94 percent of all American females in the 1965 birth cohort will be married sometime in their life. Based on another study of data from the early 1970s, the fraction of marriages that will end in divorce is 30 percent for women and 25 percent for men. Data from 1975 show that remarriage rates are 74 percent for women and 83 percent for men.

2. Research on the factors affecting fertility and its regulation have increased our understanding of the antecedents underlying changes in the fertility of individuals and society. A major emerging pattern in fertility research has been the delay of childbearing resulting in the rapid increase of first births to women over 30. In addition, there has been an increase in the proportion of women who remain childless. Another study provides support for the thesis that there is a stable preference in contemporary United States for a family of exactly two children. Voluntary contraceptive sterilization is being increasingly used in the U.S. and around the world to prevent unwanted childbearing.

3. Studies of the consequences of family size have dealt with the economic costs and benefits of children in order to examine the factors involved in one of the most critical determinants of family spacing, timing, and size. Preliminary findings on studies estimating actual expenditures on children show that the cost of children is a sizeable component of the average American family's expenditures. A child, born to a father aged 25, will (in 1981 prices) account for family expenditures of about \$62,000 during the first 18 years of life. Examining the level of expenditure by age of child, it was found that senior high school students account for about 30 percent of total expenditures, and infants 15 percent. The years age 3 to 13 are the periods of lowest cost.

4. Research on adolescent pregnancy and childbearing has shown that early childbearing has a significant economic impact on society. When it prevents individuals from achieving their educational and occupational goals, society loses their contributions to the economy and the tax base. More directly, if early childbearing leads to greater use of public services, there is a direct impact on such public sector costs as Aid to Families with Dependent Children (AFDC), Medicaid, food stamps, and foster care. The net effect of a one year increase in welfare mother's age at first birth generates an estimated saving of \$56 million in food stamp costs. The mother's age at first birth is found to affect duration of AFDC payments with a total impact of about 2.7 months shorter current duration for each year's postponement in the age of first birth. The AFDC cost savings from shorter duration are estimated as \$873 million in 1975, from a one year increase in age at first birth.

5. Few adolescent pregnancies are intended. One study found that among those in the sample who had first pregnancies, only eight percent planned them and ten percent were in the uncertain or ambivalent range; 82 percent were clearly unplanned; and 44 percent of the unplanned pregnancies were also unwanted. Thirty-nine percent of all pregnancies were unwanted; 25 percent were ambivalent; and 36 percent were wanted, with three-quarters of this last group also unplanned.

6. The impact of early pregnancy and childbearing affects not only the young woman herself and her child, but also relationships with her family and with the baby's father and his family. Usually, the families of pregnant adolescents report a sense of renewed happiness and cohesion following the pregnancy. However, observations of their interactions show the family's perceived "honeymoon" in the period surrounding the birth is followed postpartum by disillusionment and distress. In general, there are problems between the adolescent mother and the baby's father following the birth. Approximately half report feeling less close to him. Their expectations of his providing financial assistance postpartum are usually not realized. In terms of his family, his relatives were generally uninvolved in prenatal planning. In almost half of the cases there is no contact

with his family at all. Findings indicate that the adolescent may be caught in the difficult bind between her own family and the baby's father and his family.

7. A 1980-81 interview study of Mexican-origin parents in Los Angeles found that 46 percent of births were to undocumented mothers, 25 percent to mothers who were either legal residents or naturalized citizens, and 29 percent to mothers of Mexican origin born in the U.S.

mented mothers where either the mother or the father was of Mexican descent.

8. A project studied West Indian workers who migrate seasonally to southern Florida to harvest sugar cane. Of the all-male labor force, 82 percent came from Jamaica and the rest from the Eastern Carribean. Their average age is about 35 years. The vast majority are farmers from large households (six persons on the average) and have little education (under four years of schooling on the average). Of their net seasonal wages from cutting cane, about \$3,000, 23 percent are remitted to the islands. The funds transmitted are used, predominantly for the support of the worker's household.

COORDINATION AND COMMUNICATION

The activities of the Center to enhance the coordination of Federal population research programs and to foster the communication of biomedical behavioral research information in the population sciences, are presented in this portion of the report since they are coordinated in the Office of the Director.

Interagency Committee on Population Research (ICPR) enhances the coordination of population research activities supported by Federal agencies and facilitates the exchange of information and ideas among Federal programs involved with population research. The Committee is chaired by the Director of CPR, NICHD and reports to the Deputy Assistant Secretary for Population Affairs. It is comprised of representatives from the various Federal agencies concerned with research related to human population problems. The major products of the ICPR are the following two publications produced annually with the assistance of NICHD's Office of Planning and Evaluation.

Inventory and Analysis of Federal Population Research contains (1) a description of the background and role of the ICPR; (2) a statistical analysis with fiscal tables by research areas and supporting agencies; (3) a detailed inventory of all Federally supported population research projects classified according to the major research category; (4) a listing of newly started projects; and (5) a membership list of the ICPR.

Inventory of Private Agency Population Research provides information on the population research projects sponsored by the major U.S. private organizations in this field. The four principal private agencies involved with research in the population sciences, the Ford, Rockefeller, and Mellon Foundations and the Population Council, provide the data on their research projects in the same way as the Federal agencies and the information is published in the identical format as the Federal Inventory.

Population Research Monographs published by the Center through the Government Printing Office further the dissemination of information in the population sciences. These books provide a review of the state-of-the-art or report on

findings and progress in particular areas of research in the population sciences, and indicate future research directions to obtain needed knowledge.

The Center enters progress and final reports of grants and contracts selected by our Branches into the National Technical Information Service (NTIS) in order to facilitate the dissemination of information on research findings and thus further the transfer of knowledge. NTIS, part of the U.S. Department of Commerce, is being utilized since they are the central source for the public sale of scientific and technical reports of U.S. Government sponsored research and development, and they also comprise the largest documentation center in the world for the public distribution of scientific publications. The following are the most recent reports entered by the Center into NTIS:

<u>Accession No.</u>	<u>Title and Author(s)</u>
PB81-246928	The Psychology of Reproduction by Warren B. Miller
PB81-245847	Effects of Number and Timing of Births on Family Well-Being Over the Life Cycle by Sandra L. Hofferth
PB82-120940	Statistical Appendix to "Effects of Number and Timing of Births on Family Well-Being Over the Life Cycle by Sandra L. Hofferth
PB82-138884	Patterns Compared for the Voluntarily Childless, Undecided Childless, Postponing Childless and Mothers by Karen Polonko and John Scanzoni
PB82-167768	The Consequences of Being and Having an Only Child on Intelli- gence, Interpersonal Orientation, Attitudes, and Time Use by Toni Falbo
PB82-230160	Sex-Role Development and the Single Child Family by Phyllis A. Katz, Sally L. Boswell, Carol Hathaway-Clark, and Sharin Berger

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Fiscal year 1982 was marked by progress both in clinical and laboratory studies. Considerable investments in the area of LHRH analogs are beginning to suggest that this category of drugs are likely to result in a new generation of fertility regulating agents. Additionally they are proving to be of considerable potential value in the treatment of a variety of reproductive disorders. Clinical and laboratory studies in the area of barrier contraception have also been equally productive and will result in new products being available to the public. Another area in which progress has been accomplished is the drug delivery systems. One of these has undergone initial clinical testing. Although several problems have surfaced in the program, corrective steps have been implemented. Details on the overall program are presented below.

A. Product Development

Drug Development Program

The largest segment of the chemical synthesis program is directed towards the design, synthesis and testing of LHRH antagonists as antioviulatory agents. Our continuing efforts in this area have now resulted in the development of analogs that are active in blocking ovulation in the rat at subcutaneous dose levels below 1.0 microgram. This technical breakthrough resulted from the incorporation of D-arginine into the 6-position of previously potent LHRH antagonists. Concomitant is the observation, for the first time, of oral activity at modest dose levels (2 milligrams) in the rat. We therefore visualize the possibility of increasing oral activity of these antagonists through further chemical modifications and/or drug formulation. As potent gonadotropin inhibitors, these LHRH antagonists also have the potential of acting as antispermatic agents. Exploration of safety in animal models and preliminary clinical studies in men and women are being pursued.

The safety of two LHRH agonists is undergoing in-depth evaluation in animal models. Ninety-day toxicology study on one analog, [(im-Bzl)-D-His⁶,des-Gly¹⁰] LHRH ethyl amide, has been completed in rats and rabbits. No adverse findings were observed other than calcification of testes in rats which has been observed with other LHRH agonists. Similar evaluation of (D-Trp⁶,des-Gly¹⁰)LHRH ethyl amide is in progress. The effect on rat testes can be reversed by the concomitant administration of testosterone.

A number of derivatives of gossypol have been synthesized and tested as potential male antifertility agents. It is hoped that they will be active without the known toxic properties associated with gossypol itself. Thus far none of the gossypol analogs or intermediates have shown antispermatic properties in vivo, but several have shown inhibition of sperm motility in vitro.

The synthesis of prostaglandin analogs as potential luteolytic agents, which has been ongoing for a number of years, has yielded two analogs worthy of non-human pri-

mate studies. During the next year these analogs will be synthesized in sufficient quantity to be evaluated in a recently developed primate model. No further syntheses of new analogs is anticipated at this time.

An area that is continuing to receive support is the pursuit of antiprogestational agents. A variety of different steroidal modification are being pursued, e.g., D-seco steroids, derivatives of 5 α -dihydro-norethindrone, 17 α -substituted progesterone derivatives and 7 β -methylretrotestosterone.

Synthetic Chemical Facility

The facility continues to play a major role in the drug development program. During FY 1982 a variety of unnatural amino acids such as 3-(2-naphthyl)-D-alanine, Boc-4-chloro-D-phenylalanine, L-3,4-dehydroproline, and 2- and 4- pyridyl-D-alanine were synthesized. The availability of these amino acids to our contractors working in the LHRH antagonist area has greatly accelerated progress. A variety of steroids have also been synthesized, e.g., (-)-6- and (-)-7-methylnorgestrel (from levonorgestrel) as potential long acting progestins; long acting esters of levonorgestrel and syn- and anti-oximes of levonorgestrel esters and steroidal intermediates for use by other contractors working in the antiprogestational area. Finally, a multi-step synthesis of gram quantities of 16-fluoro-13-dehydro-PGF₂ is underway for eventual testing as a luteolytic agent in a non-human primate model.

Biological Drug Testing Facility

The biological testing facility continues to assess some four hundred compounds annually for antifertility and classical endocrine activities. A long term study is currently underway in rhesus monkeys to evaluate the pharmacokinetic and antifertility activities of several new esters of norgestrel. It is anticipated that results from this study will permit the selection of a single compound for animal safety evaluation. This aspect of the testing program is part of a collaborative WHO/NIH effort to develop improved injectable long-acting drugs. Because of a reported association between progestational agents and a lowering of HDL cholesterol, several long-acting injectable steroids are being studied in cynomolgus monkeys for their effect on lipid profiles.

In addition to the evaluation of long-acting drugs for the purpose of female fertility regulation the facility is testing some of these drugs in the male as potential antifertility agents. Considerable inhibition of testes function has been observed with some of the long-acting progestins. Recognizing that androgen substitution will be required in the event that either LHRH analogs or progestins become useful male antifertility agents we have begun a more intensive evaluation of testosterone esters. Employing several different formulations of new esters, more sustained blood levels of testosterone have been observed than those achieved with testosterone enanthate.

Drug Delivery Systems and Oral Formulations

Development of biodegradable drug delivery systems reached a number of milestones during this past year. As a result of the successful Phase I clinical evaluation of the Capronor tubular capsule implant, a chronic toxicological evaluation is being implemented which will support a one year Phase II clinical study for safety and ef-

ficacy. At the other end of the spectrum, injectable microcapsules of polylactide containing levonorgestrel have also been shown in animal studies to be worthy of further development. Therefore, large batches will be made so that chronic toxicology can be evaluated. Since the microcapsules cannot be retrieved after injection it will be necessary to proceed directly to chronic studies, at least one year, in animals rather than the sub-acute study (90-day) which was done for Capronor.

On the negative side, after many years of development and evaluation of the poly(ortho ester) known as ALZAMER in animals, a second local irritation study in humans was conducted by WHO which, this time contained levonorgestrel (BIDS-NOG). Unfortunately, the itching and swelling which had occurred sporadically in animal models and humans for BIDS-NET also occurred with BIDS-NOG. Six out of ten subjects had itching ranging from minor to severe and two out of the ten had swelling up to 2 cm. Progress has been made, however, on a back up polymer for bioerodible delivery systems. Since this type of system does not depend on diffusion which is drug/species dependent it is far easier to adapt for new drug entities. Therefore, evaluation of this alternative polymer will now be accelerated.

Evaluation of a new oral dosage form for synthetic steroids which would lower the body burden by providing sustained release has also run into difficulties. Stability of norethindrone in the glyceride matrix which provides the timed release was inadequate and an improvement was made by switching to norethindrone acetate. Subsequently, clinical studies showed that slow release of ethynyl estradiol resulted in a high degree of sulfation particularly at C-3. Substitution of mestranol appears to have helped. A clinical evaluation in eighteen subjects using a cross-over design in comparison to a standard oral contraceptive is underway.

Phase I Clinical Trials of a new combination oral contraceptive containing estradiol as the estrogenic component and (\pm)-norgestrel, as the progestational component, will be initiated shortly. The main objective of the study will be to determine the optimal ratio of estradiol and (\pm)-norgestrel to ensure uniform inhibition of ovulation, cycle control and minimal side effects. This formulation is unique in that it incorporates a natural estrogen, estradiol, in an oral contraceptive. (\pm)-Norgestrel is currently marketed in the United States alone or in combination with ethynyl estradiol as an oral contraceptive.

Barrier Methods of Contraception

The one year recruitment phase of a multi-clinic Phase III clinical trial of a polyurethane sponge diaphragm (Secure) has been completed. The one year follow-up phase is ongoing. Data show that in comparison with the currently available diaphragm, there are no significant differences in the performance rates for the two methods. Additional follow-up is required before the results can be conclusive. The sponge users appear to be highly enthusiastic about the device, and it is expected that within a year, contraceptive sponges may be on the market for general use.

The study to evaluate the contraceptive effectiveness of the cervical cap has been initiated. The original protocol called for a comparison of the Prentif cap, Vimule cap, and the diaphragm. However, there were some problems reported with the Vimule with regard to the development of frank lesions in the vagina which appeared to be related to cap size and duration of wear. The device was withdrawn from the study.

To date, no adverse effects have been observed with the Prentif cap.

A Phase II clinical evaluation of Contracap, a custom-fitted cervical cap with a one-way valve which allows the cap to remain in place indefinitely, was terminated due to excess of pregnancies. Final analysis of the data is not complete but it appears that dislodgements which could be attributed to poor fitting technique by the investigators may be partially to blame. On the other hand, some of the pregnancies occurred in wearers who had not experienced dislodgements at all and whose caps, therefore, were undoubtedly in situ during coitus. The developer is currently working on an improved cap design and on better fitting procedures at no expense to the government.

Development of new designs for more conventional cervical caps, i.e. presized and for intermittent use, is proceeding. Prototypes have been constructed and attempts are being made to quantitate the forces required to dislodge the cap.

Work on the development of a disposable diaphragm is progressing well. A device based on a polyether-polyurethane has been tested and when plasticized with polyethylene glycol it releases nonoxynol-9 with an initial burst followed by sustained release. Animal studies in rabbits and baboons are encouraging and clinical evaluation is anticipated within a year.

Preclinical evaluation of a new spermicidal contraceptive is presently ongoing. Besides having greater spermicidal potency than presently available surfactant materials, the new compound may have certain unique properties. It appears to bind to the sperm, enter cervical mucus more readily, and causes disruption of the sperm membrane. Studies in monkeys indicate that it may be active for as long as 12 hours in the vagina. Most of the presently available spermicidal formulations are only active for 20 minutes up to one hour. Recognizing that a vaginal spermicidal preparation with long-acting properties would be an important addition to the armamentarium of barrier methods, we are supporting the development of a new formulation of nonoxynol (suppository) which will be effective for at least 16 hours. Release studies in animals are planned for the next fiscal year.

Injectable Contraceptive

Clinical trial of norethindrone enanthate as a long-acting injectable progestin is in its final planning stage. Initial discussions with the FDA suggested that results of a two year study involving 200 subjects would satisfy the filing of a NDA. Additional discussions with the FDA are in progress to ascertain whether the scope of clinical studies in the USA can be reduced in view of the extensive studies on the efficacy of norethindrone enanthate conducted by the WHO.

Clinical Studies with LHRH Analogs

Clinical studies with three different LHRH agonists have been in progress for the past two years. These studies involve both men and women volunteers and are designed not only to provide us with the clinical pharmacology of these drugs, but also to identify possible contraceptive approaches.

In female volunteers, administration of agonists during early luteal phase results in lowered progesterone levels, but without effect on duration of cycle. Mid luteal

phase administration lowers progesterone levels and shortens the cycle by 2-3 days. The luteal phase administrations were aimed at establishing a luteolytic approach. At the present time it does not appear that this approach will be practical.

Administration of agonists during follicular phase has produced variable results. Short term administration, one to two days, during early follicular phase has resulted in delayed ovulation and prolongation of the cycle. Late follicular phase administration appear to have little effect. Studies are in progress to evaluate the effect on ovulation of more frequent administration of the agonists during follicular phase. Information generated during the previous fiscal year indicated that continuous administration of the agonist does block ovulation. A study has been initiated in which the agonist is administered for a period of three weeks together with a progestin given during the 3rd week. The aim of this study is to determine whether spontaneous controlled withdrawal bleeding can be achieved in a manner similar to oral contraceptives.

Two studies on the use of agonists in male volunteers have been completed. In one of the studies a 50 µg dose of D-Trp⁶-Pro⁹-N-Ethylamide-LHRH was given to normal volunteers every fourth day for 10 weeks. This regimen was based on prior studies in the rat where pronounced effects on spermatogenesis were observed. Intermittent administration of the drug did not produce a consistent suppression of the pituitary-gonadal axis. In a separate study involving daily administration of 50 µg of the same drug together with 100 mg of testosterone enanthate every other week for a period of 20 weeks, there were no toxic effects observed. Sperm production was depressed to oligospermic levels without a drop in libido. All of these studies indicate that doses of the agonists greater than 50 µg will be required to achieve effective suppression of spermatogenesis and that testosterone enanthate will have to be given to maintain normal libido.

Studies in male volunteers employing the D-Nal(2)⁶LHRH analog have been initiated. At the 100 µg dose the gonadotropin responses are essentially flat by day 7. Data on testosterone suggest a progressive drop in blood levels. A study is in progress to evaluate the effect of 200 µg of this drug over a period of 16 weeks. This dose is considerably higher than the ones used in our previous studies. Data should become available during the next fiscal year.

Distribution Program

The CBD continues to distribute various reagents to the scientific community. We continue to experience a steady demand for all of the reagents for which we are responsible. It is a productive, cost effective program that has a significant effect on the course of basic and applied research.

B. Directed Fundamental Research

RIA Development

Reagents for the radioimmunoassay of monkey luteinizing hormone are now available and are being sent to qualified investigators. There is sufficient material to make up over 350 kits, each consisting of 15 µg of cynomolgus LH, 0.55 ml of R13 antiserum, and 40 µg of rhesus LH standard. Additionally, 4 mg of highly purified LH have been

isolated from cercopithecus monkey pituitary glands, which serves equally well as a tracer. Further supplies of cynomologus LH and anti-hCG antisera have been accumulated which when completely characterized will increase the number of kits to be distributed.

In the meantime, since the demand for these kits is high, a continuous supply of pituitary glands is being sought to assure future availability of these reagents.

All the materials needed to assemble the 100 kits for the radioimmunoassay of rat androgen binding protein have been collected. In addition, they have been shown to function properly. There appears to be some difficulty in preparing the tracer and displacement standard in a form that is convenient for shipping. Attempts to lyophilize the materials resulted in a loss of binding and displaceability. It is hoped that by the end of the contract period, the problem will be solved.

Gonadocrinin

Isolation of gonadocrinin, an ovarian peptide with LHRH like activity obtained from PMSG stimulated rat ovaries, has been terminated because of inconclusive results. Materials isolated from the ovaries had HPLC profile similar to one of the synthetic superagonists or native LHRH. The quantity that could be isolated varied from batch to batch of the ovaries. It is possible that the material is of endogenous origin and corresponds to native LHRH, or behaves as native LHRH in the chromatographic systems employed to date. On the other hand it may indeed represent contamination of the ovarian extracts in the laboratory. Attempts are being made to look for this material in porcine follicular fluid.

C. Collaborative Efforts

The development of improved fertility regulation methods is a very complex and expensive process. It begins with the generation of new ideas and approaches and goes through an intensive R & D program which culminates in a new product or approach. At each step along this tortuous pathway an agency is faced with numerous difficult decisions and problems which are fiscal, scientific and administrative in nature. The CDB has recognized that in order to achieve a greater chance for success it is critical that we collaborate with the other contraceptive development agencies, with pharmaceutical firms as well as with the rank and file scientific community both within and outside of NIH. Specifically we have a close collaboration with the Intramural Research Program in the area of LHRH analogs and concerning all aspects of primate reproduction and its regulation. This has been a very useful interaction with direct benefits to both programs.

In several sections of this report we have stressed our collaboration with the WHO. This collaboration has been very extensive and ranges from joint consultations to joint product development. It can serve as a model for what can be accomplished under circumstances where agencies join forces and recognize the specific capabilities and achievements of the respective programs. The necessarily high cost involved in the development of new contraceptives can thus be shared and numerous obstacles can be surmounted more readily.

We anticipate that additional collaborative efforts with the Agency for International Development and the Population Council will be implemented during the next fiscal year.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : A Study of the Use of Biodegradable Polymers for the Sustained Delivery of Contraceptive Drugs
Contract No. : N01-HD-3-2741
Contractor : Research Triangle Institute
Money Allocated: \$298,347 (FY 73 for two years); \$185,262 (FY 75);
\$224,082 (FY 76); \$211,983 (FY 77); \$210,081 (FY 78);
\$306,740 (FY 79); \$258,688 (FY 80); \$213,383 (FY 81);
\$137,668 (FY 82)

Objectives: To develop a biodegradable polymer reservoir for subdermal delivery of a contraceptive steroid, e.g. levonorgestrel, for periods of one year or longer. The device is designed to provide constant release rate by diffusion control and to biodegrade after the drug is exhausted.

Major Findings: The first clinical trial of Capronor, conducted at Duke University Medical Center, was completed. The study spanned 5 menstrual cycles: three observation cycles to confirm ovulation, one with the capsule implanted, and a follow-up observation cycle. Serum hormone and levonorgestrel levels, and suppression of ovulation in 7/8 subjects, demonstrated sustained release. No serious adverse effects were encountered. The procedure for the RIA of levonorgestrel was optimized.

A new batch of poly(ϵ -caprolactone) tubing was prepared using a higher molecular weight polymer intended to remain functional for > 1.5 years. The M_n at which capsule fragmentation becomes probable was shown to be 20,000, based on both in vitro and in vivo tests. ϵ -Hydroxycaproic acid was confirmed to be the major urinary and fecal metabolite of poly(ϵ -caprolactone) in rat.

Diffusional loss of ethyl oleate from Capronor was determined to be 1 mg per month per cm capsule length; this rate will not cause premature loss of the vehicle. Stability studies showed that ethyl oleate is subject to autoxidation when Capronor is stored for prolonged times at 5°C. This process is more rapid at 37°C. Studies of the stabilizing effect of the antioxidant d,l- α -tocopherol are in progress and the alternative use of tricaproin as a suspending vehicle is also being investigated.

Significance to Biomedical Research and Program of the Institute: Development of drug delivery systems for contraceptive drugs is one of the stated goals of the Contraceptive Development Branch.

Proposed Course: This is expected to be a continuing contractual effort leading to the development of improved contraceptive technology.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Development of a Long-Acting Injectable Contraceptive

Contract No. : N01-HD-5-2817

Contractor : Schering AG

Money Allocated: \$1,211,168 (FY 75) 3 years; \$120,000 (FY 78); \$142,477 (FY 79);
\$88,782 (FY 80); \$280,917 (FY 81); \$89,881 (FY 82)

Objectives: The purpose of this contract program is to acquire sufficient data to support the filing of a New Drug Application (NDA) for norethindrone enanthate, a long-acting progestational agent. This requires support of preclinical, clinical and long-term drug safety studies.

Major Findings: Long-term drug safety studies continue in dogs and monkeys. No unusual findings have been encountered other than those known to be associated with progestational drugs in these species. One monkey was reported to have a uterine carcinoma but the precise nature and origin of this lesion remains unclear.

A two-year rat study in which norethindrone enanthate intramuscularly and a marketed oral preparation of norethindrone and mestranol are being given at dose levels equivalent to 1, 10 and 50 times the human contraceptive dose for each drug has been initiated. Satellite groups are being used to measure blood levels of norethindrone throughout the study. This study should permit a correlation between the body burden of the drug following two routes of administration and any observed pathology.

Efforts are currently underway to determine whether the Food and Drug Administration may alter its requirement for large scale clinical trials of this drug in the United States in view of the extensive clinical experience elsewhere in the world.

Significance to Biomedical Research and Program of the Institute: The development of a long-acting injectable contraceptive is directly related to the goals of the Contraceptive Development Branch.

Proposed Course: This is expected to be a continuing contractual effort encompassing completion of all preclinical and clinical requirements for the filing of a New Drug Application (NDA) and long-term drug safety studies in dogs and monkeys.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : New Biodegradable Drug Delivery Systems
Contract No. : N01-HD-7-2825
Contractor : ALZA Corporation
Money Allocated: \$206,289 (FY 77); \$204,284 (FY 78); \$455,411 (FY 79)
\$356,612 (FY 80); \$87,102 (FY 81); \$58,316 (FY 82)

Objectives: The BIDS-steroid project is a collaborative effort of WHO, NICHD and the ALZA Corporation. It has as its objective the development and clinical testing of an implantable bioerodible steroid contraceptive for women with an effective duration of 4-6 months per implant.

Major Findings: During the current period the potential for local irritation of a number of formulations of BIDS was tested in cynomolgus monkeys. Only the group of monkeys exposed to the norgestrel containing systems (BIDS-NOG) exhibited no reaction or migration of systems. Newly manufactured sterile BIDS-NET exhibited migration but no irritation. All other formulations exhibited some irritation in a few monkeys.

It was decided to concentrate efforts on the development of a levonorgestrel system, and the project produced two BIDS-formulations (BIDS-placebo and BIDS-NOG 19) under very clean conditions in the ALZA pilot plant and in a sterile facility at CIBA-GEIGY, Basel. All testing was performed at ALZA. A total of 177 BIDS-NOG 19 and 171 BIDS-placebo were packaged and radiation sterilized. Of these, 90 each were stored at CIBA-GEIGY, Basel for the use of WHO in local irritation studies which were conducted in London and Rome and for future use in Phase I studies. Preliminary reports from these studies indicated that two out of five subjects at one center showed significant local irritation (swelling and erythema) and two more had some itching. At the other center two out of five subjects had some itching but there was no swelling or redness.

Significance to Biomedical Research and Program of the Institute: Development of new drug delivery systems for contraceptive drugs is one of the goals of the Contraceptive Development Branch.

Proposed Course: Data from the local irritation study conducted by WHO indicated and described above indicate that although this product does not present any evidence of health hazards, it is not a viable approach at this point in time. If the manufacturer can resolve the local irritation problem, additional testing would be considered.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Development and Testing of New Biodegradable Drug Delivery Systems
Contract No. : N01-HD-7-2826
Contractor : SRI International
Money Allocated: \$149,786 (FY 77); \$237,555 (FY 78); \$270,465 (FY 79)
\$238,768 (FY 81); \$249,391 (FY 82)

Objectives: It is proposed to develop non-toxic biodegradable polymers capable of delivering a contraceptive agent with zero order kinetics for at least a six-month period. Additionally, drug release and polymer solubilization should take place concomitantly so that rate of drug release is controlled by the rate of polymer dissolution.

Major Findings: During this contract year a facile synthesis of the diketene acetal 3,9-bis(ethylidone 2,4,8,10-tetraoxaspiro[5,5]undecane) referred to as DETOSU has been developed and the condensation of DETOSU with mixtures of trans-cyclohexanedi-methanol and 1,6-hexanediol has been standardized so that poly(ortho esters) having any desired molecular weight up to about 100,000 and glass transition temperatures between 20 and 110°C can be routinely prepared. It has also been determined that hydrolysis of the polymer produces the expected products and that radiation sterilization at 2.5 mrad produces no significant changes in the polymer nor does any levonorgestrel attachment to polymer take place.

Levonorgestrel release studies from devices containing 30 wt% drug and 10 wt% Na₂CO₃ have shown considerable data scatter which is at least partly due to sample inhomogeneity caused by hand-mixing. This has now been greatly improved by the construction and use of a Brabender-mixer dedicated to this project. However, it has also been found that above approximately 130°C the polymer is not thermally stable and decomposition with generation of an acidic species appears to take place. Therefore, fabrication at temperatures above 130°C significantly accelerates polymer erosion rate. Furthermore, the samples also contain bubbles which may arise from polymer decomposition during fabrication. Clearly, future devices will need to be fabricated below 130°C.

In vivo studies in rabbits have now been underway for more than 120 days and despite considerable scatter, blood plasma levels of levonorgestrel of about 0.15 ng/ml and 0.25 ng/ml have been maintained in animals with one and two implants respectively.

Significance to Biomedical Research and the Program of the Institute: The work undertaken in this project is directly relevant to the published purpose of the Contraceptive Development Branch to support research directed towards development of new methods of contraception.

Proposed Course: This project is expected to be a continuing contractual effort leading to the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Development of a Radioimmunoassay for Rhesus Monkey Luteinizing Hormone
Contract No. : N01-HD-7-2829
Contractor : University of Pittsburgh
Money Allocated: \$66,331 (FY 77); \$65,160 (FY 78); \$91,664 (FY 79); \$108,160 (FY 80)

Objectives: The aim of the program is to develop a radioimmunoassay for rhesus monkey luteinizing hormone (LH) and to provide sufficient reagents to prepare 200 kits (15,000 tubes per kit) for distribution to the scientific community.

Major Findings:

1. On November 23, 1981, 5175 μ g of cynomolgus LH for radioiodination and 192 ml of anti-hCG serum R13, pool D, were shipped to Dr. A.F. Parlow for vialing. Prior to shipment of these materials, testing of the tracer produced by radioiodination of several lyophilized aliquots of the cynomolgus LH showed it to be of poor quality compared to that prepared from unlyophilized material. For this reason, we decided to distribute cynomolgus LH, as well as the R13 antiserum, in the form of frozen solutions. The vialled reagents were returned to the NICHD, and macaque LH RIA kits, each consisting of 15 μ g of cynomolgus LH, 0.55ml of R13 antiserum, and 40 μ g of rhesus LH standard, are now being sent to qualified investigators.

2. Four mg of highly purified LH have recently been isolated from 825 cercopithecus monkey pituitary glands. This material is comparable to the preparation of highly purified cynomolgus LH, and, following radioiodination, serves equally well as a tracer with both the R13 and the R132 anti-hCG sera. Appropriate fractions from the earlier purification of cynomolgus LH have been combined to provide about 60 mg of a cynomolgus LH reference preparation. The new reference preparation is free of subunits and contains approximately 4% LH; its bioactivity: immuno-activity ratio is identical to that of the rhesus LH reference preparation and to that of rhesus serum LH.

The accumulation of additional bleedings from rabbit #132 has increased the size of this antiserum pool from 163 ml to over 400 ml. When used at a final dilution of 1:25,000, this pool of R132 binds about 14% of cercopithecus LH tracer. With these reagents, the sensitivity and specificity are similar to those of the cynomolgus LH:R13 system, except for a greater cross-reactivity of R132 with LH beta subunit, which does not appear to present a problem.

Significance to Biomedical Research and Program of the Institute: The work to be undertaken in this project is directly relevant to the published purpose of the Contraceptive Development Branch to acquire specific substances concerned with aspects of reproduction processes that are subject to experimental interventions.

Proposed Course: Completed

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Development of Orally Active Dosage Forms for Steroids

Contract No. : N01-HD-7-2831
Contractor : Southwest Research Institute
Money Allocated: \$95,027 (FY 77); \$104,104 (FY 78); \$323,500 (FY 79);
\$280,883 (FY 80); \$58,291 (FY 81); \$168,300 (FY 82)

Objectives: The aim of this program is to prepare sustained-release oral formulations of contraceptive steroids by incorporating these products in microspheres and to determine whether this dosage form will minimize daily peaks of the drugs and reduce body burdens while maintaining contraceptive efficacy and clinical acceptability.

Major Findings: Studies have continued over the past year on the development and evaluation of sustained-release microspheres containing norethindrone acetate (NET-acetate) in place of norethindrone (NET) and mestranol (ME) in place of ethynyl-estradiol (EE).

While sustained-release dosage forms of NET in a mixture of mono- and diglycerides gave desirable pharmacokinetic results in clinical studies, the dosage form did not have good long-term aging stability at 37°C as indicated by changes in the in vitro release rates. The cause of the problem appeared to be the precipitation of the NET in the matrix during aging which affected the release rate. As a result, NET-acetate was substituted for NET it was expected that the NET-acetate, being more soluble in glycerides, would give a more stable dosage form. Data have indicated that indeed a more stable dosage form results.

Ethynylestradiol (EE) undergoes a very high degree of sulfation in the intestine when given in the slow release form. In order to avoid excess sulfation, which occurs primarily in the 3-position of EE, mestranol was substituted since its 3-position is blocked by a methoxy group. Initial clinical studies indicate that ME in a sustained-release dosage form may produce desirable sustained-release levels of EE. Additional clinical evaluation of NET-acetate and ME containing microspheres in comparison to a standard oral contraceptive has been planned.

Significance to Biomedical Research and the Program of the Institute: The work undertaken in this project is directly relevant to the published purpose of the Contraceptive Development Branch to support research directed towards development of new methods of contraception.

Proposed Course: This is expected to be a continuing contractual effort leading to the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Folliculogenesis in the Rhesus Monkey During the Menstrual Cycle
Contract No. : N01-HD-7-2835
Contractor : George Washington University
Money Allocated: \$45,999 (FY 77), \$22,204 (FY 78), \$57,818 (FY 80), \$4,822 (FY 81)

Objectives: Preantral follicles are the initial pool from which to dominant follicle is recruited and little is known as to how their development relates to the hormonal changes that occur during the 28-day menstrual/ovarian cycle. This study was undertaken to determine the status of preantral follicles at various stages during this cycle.

Major Findings: Ovaries obtained from eighteen adult regularly cycling rhesus monkeys were evaluated to determine the status of preantral follicles development at various stages throughout the menstrual cycle. The ovaries were serially sectioned and all preantral follicles on every 20th section were classified, counted and/or measured. Antral follicles and ovarian vein progesterin levels for these same monkeys were previously presented (Koering, 1969, Resko et al., 1975).

Results from this recent study show that a variation in the number of primordial follicles exists between monkeys, but each ovary of a pair were similar. There was also a significant increase in the mean percentage of developing preantral follicles in size groups >100 μ in diameter during the periovulatory period. However, atresia was seen in follicles >35 μ in diameter but it was less than 4% of the pool for each size group and no significant differences existed between the stages of the cycle. The presence of polyovular follicles was characteristic of some monkeys but there was not relationship to age or the stages of the cycle.

These data suggest: 1. there is no difference in the number of developing preantral follicles in various size groups between the right and left ovaries even though the primordial follicles decrease in number with time showing neither ovary has pre-dominance over the other. 2. that developing preantral follicles >100 μ in diameter are sensitive to the unique hormonal milieu present during the periovulatory period. 3. atresia is minimal in preantral follicles and shows no relationship to time in cycle. 4. polyovular follicles can be a distinguishing feature of certain adult monkeys.

Significance to Biomedical Research and Program of the Institute: Since the ovarian follicle is the target for contraceptives, the knowledge of its natural history is important for appreciation of the possible mechanisms of action of contraceptives.

Proposed Course: Research has been completed and the contract will be terminated in FY 1982.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Biological Testing Facility

Contract No. : N01-HD-8-2813 continued as N01-HD-0-2846

Contractor : Mason Research

Money Allocated: \$700,623 (FY 78); \$845,501 (FY 79); \$156,490 (FY 80);
\$839,980 (FY 80 under N01-HD-0-2846); \$1,085,506 (FY 81);
\$1,178,083 (FY 82); \$1,278,131 (FY 83); \$1,386,882 (FY 84)

Objectives: The objective of this contract program is the establishment of a biological testing facility capable of broad spectrum evaluation of new drugs and devices and rapid exploitation of potential leads in the control of fertility. Sources of compounds for testing include contract synthetic programs supported by the CDB and numerous private, public and governmental laboratories throughout the world. The staff of the CDB reviews all compounds submitted for evaluation to determine the precise manner in which each drug will be studied.

Major Findings: The testing facility continues to evaluate new drugs, formulations and delivery systems in an efficient manner and has extended its capabilities to include radioimmunoassay of natural and synthetic steroids.

Emphasis continues to be placed on the screening of potent new analogs of LHRH. Both antagonists and agonists have been identified which exhibit biological activity with as little as a few micrograms.

New esters of norethindrone and norgestrel continue to be evaluated for duration of estrus suppressing activity and several candidate compounds are being studied in rhesus monkeys. The effects of vehicle and particle size distributions in aqueous suspension are also being investigated. Esters of testosterone are being screened for duration of androgenic activity.

Selected esters of norgestrel are being studied for their effect on reproductive organs and performance in the male.

Significance to Biomedical Research and Program of the Institute: The heart of any drug development program is the rapid identification of biological activity and exploitation of promising leads. The ability of the CDB to evaluate compounds and devices in a uniform manner is of great importance to our contract synthetic program and the stated goals of the Branch.

Proposed Course: This is a continuing contractual effort leading toward the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Synthesis and Testing of Novel Steroids with Potential Male
Contraceptive Activity
Contract No. : N01-HD-8-2815
Contractor : Laval University
Money Allocated: \$33,812 (FY 78); \$37,178 (FY 79)

Objectives: The objective of this contract is to synthesize 11-aza-5 α -dihydrotestosterone analogs which will lead to the study of a distinctly 11-hetero steroid. The importance of the 11-position in governing both estrogenicity and effects on gonadotrophin is now apparent. These compounds will be tested for the male contraceptive activity.

Major Findings: The synthesis of 11-aza-5 α -androstane-3,17-dione has been accomplished from adrenosterone. Birch reduction of the latter gave 5 α -androstane-3,11,17-trione which was diketalized to the 3,17-bisethylenedioxy derivative, reduced with lithium aluminum hydride to the 11 β -alcohol, and dehydrated to the 9,11-olefinic product with thionyl chloride. Ozonolysis of the deketalized product (80% yield) and oxidation of the resulting 9,11-seco 3,9,17-trioxo-11-aldehyde with Jones reagent gave the corresponding seco triketo acid which was converted with oxacyl chloride to its chloride and thence with sodium azide to its azide which was treated without purification with aqueous acetic acid at elevated temperature to yield 11-aza-5 α -androst-9(11)-ene-3,17-dione (overall yield from the triketo seco acid ~20%). Reduction with cyanosodium borohydride, followed by Jones' oxidation gave in practically quantitative yield 11-aza-5 α -androstane-3,17-dione which should be readily convertible by conventional methods to the target products of this project. [Reduction of the imine with hydrogen and PtO₂ was less satisfactory]. In parallel experiments a number of steps in the previously elaborated route to 3,9,17-trioxo-9,12-seco-11-nor-5 α -androstan-12-oic acid, from hecogenin, were performed, in part with the cooperation of the pilot-plant team of Ayerst Laboratories, Montreal - the 9,12-seco 12-acid being also convertible to 11-aza steroids.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly relevant to the purposes of the Contraceptive Development Branch to support the synthesis and evaluation of novel steroidal compounds for contraceptive utility.

Proposed Course: This is the terminal year for this contract.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Primate Testing Facility

Contract No. : NO1-HD-9-2838

Contractor : Hazleton Laboratories America, Inc.

Money Allocated: \$906,286 (FY 79) 3 years

Objectives: The objective of this contract program is the establishment of a primate testing facility for evaluation of the clinical potential of new contraceptive drugs, formulations and delivery systems. The present colony consists of 120 female and 31 male *Cynomolgus* monkeys (*Macaca fascicularis*). Initially they will be used to study potent analogs of LHRH and prostaglandins. The data derived from studies at this facility will determine, to a large degree, whether the institution of clinical trials is warranted.

Major Findings: The use of chorionic gonadotrophin treated animals continues to be examined as a reliable predictor of luteolytic activity in *cynomolgus* monkeys.

A local irritation study revealed that bioerodible implants designed to deliver norgestrel or norethindrone produced little or no host reaction.

Studies have been instituted to assess the effect of several long-acting esters of norgestrel on lipid profiles.

The luteolytic activity of a synthetic prostaglandin is being evaluated in normal and gonadotrophin treated animals.

Significance to Biomedical Research and Program of the Institute: Evaluation in subhuman primates is absolutely essential to establish the clinical potential of new contraceptive modalities before undertaking the extensive and costly safety studies required for clinical trials. Additionally, certain drugs appear to exhibit substantially different pharmacological properties in primates and in small laboratory animals thus limiting the utility of the latter. The ability of the CDB to evaluate compounds in subhuman primates is of great importance to our contract synthetic program and the stated goals of the Branch.

Proposed Course: This is expected to be a continuing contractual effort leading to the development of new contraceptive modalities and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Clinical Pharmacology of LH/FSH-RH Analog
Contract No. : N01-HD-O-2800
Contractor : Laval University
Money Allocated: \$280,300 (FY 80), \$427,615 (FY 81)

Objectives: The objective of this contract is to investigate the potential of intranasal administration of D-Ser(TBU)⁶-desGly-NH₂¹⁰-LHRH-EA as an antioviulatory and luteolytic drug in women.

Major Findings: A detailed dose-response of plasma LH and FSH levels following the administration of the LHRH agonist [D-Ser(TBU)⁶,des-Gly-NH₂¹⁰]LHRH ethylamide (LHRH-A) by nasal spray shows that a maximal response is obtained at doses ranging between 200 and 500 µg, when the peptide is administered early in the follicular phase or between days 6 and 10 of the luteal phase. Comparison with the subcutaneous route of administration in the early follicular phase shows that the efficiency of the intranasal route is 3 to 5% as compared to that obtained after subcutaneous injection. Analysis of the time of maximal sensitivity to administration of the peptide (2 doses intranasally in a single day) during the luteal phase shows that although decreased progesterone levels follow administration of the LHRH agonist during the first 4 days of the luteal phase, there is no effect on the length of the cycle. However, when the peptide is administered between days 6 and 10, serum progesterone levels are decreased and menstruations occur early (2-3 days earlier), thus indicating luteolysis. When the peptide is administered on a single day between days 4 and 14 of the follicular phase, marked and variable changes of the time of ovulation and/or length of the luteal phase are observed. Such treatment leads, in some cases, to disturbed post-treatment cycles. Study is now in progress of the effect of daily administration of the peptide during the first 21 days of the cycle followed by 5 days of progestagen treatment in order to maintain regular cycles and avoid over-suppression of the pituitary ovarian axis.

Significance to Biomedical Research and Program of the Institute: Development of new contraceptive drugs is one of the major goals of the Contraceptive Development Branch.

Purposed Course: Delays in volunteer recruitment will necessitate extension of research to FY 1983.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Clinical Pharmacology of LH/FSH-RH Analog
Contract No. : N01-HD-0-2811
Contractor : Syntex Research
Money Allocated: \$778,226 (FY 80), \$1,152,437 (FY 81), \$120,951 (FY 82)

Objectives: The objectives of this contract are to assess: 1) safety of the Syntex agonist; 2) to ascertain its potential for fertility regulation in men and women.

Major Findings: Studies continue on the D-Nal(2)⁶ analogue of LHRH. Over the past year, slight delays have been experienced in the synthesis of the large quantities necessary for clinical trials, although the basic problems now appear to be resolved. A satisfactory intranasal formulation has been prepared and a bioavailability study comparing various routes of administration is in analysis. Longer term toxicity studies are in progress (awaiting analyses) and various breeding and teratological studies have been completed. Data generated so far have failed to excite concern on the part of FDA.

Preliminary clinical trials on males at Harbor General Hospital are encouraging. Gradual desensitization of the pituitary is apparent; at the 100 µg dose the gonadotrophin responses are essentially flat by day 7. Data on testosterone suggest a progressive decrease in secretory rates with time. Studies of increased doses and longer time periods have been initiated.

Studies in women with tubal ligation carried out at UCSF suggest a delayed ovulation and a prolonged cycle when drug is administered during the early follicular phase. The cycle was also lengthened by early luteal phase administration. Ovulation inhibition studies have started.

Significance to Biomedical Research and Program of the Institute: Development of new contraceptive drugs is one of the major goals of the Contraceptive Development Branch.

Proposed Course: Research should be completed in FY 1983.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Synthesis of Luteolytic Agents

Contract No. : N01-HD-0-2813

Contractor : Indiana University Foundation

Money Allocated: \$82,074 (FY 80); \$87,841 (FY 81)

Objectives: The objective of this project is to synthesize 12-fluoro- and 12-hydroxy-prostaglandin analogs related to natural $\text{PGF}_{2\alpha}$ which might prove to be better luteolytic agents.

Major Findings: The total synthesis of (+)-12-hydroxy $\text{PGF}_{2\alpha}$ methyl ester and (+)-12-hydroxy-13,14-dihydro $\text{PGF}_{2\alpha}$ methyl ester is near completion. The synthesis of (+)-15-epi-12-fluoro $\text{PGF}_{2\alpha}$ methyl ester (606 mg) has been completed. All of these analogs will be subjected to luteolytic assays.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly relevant to the purposes of the Contraceptive Development Branch to support the synthesis and related analogs for contraceptive utility.

Proposed Course: This is expected to be a continuing contractual effort leading toward the development of new chemical contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : New Antiprogestational Agents

Contract No. : N01-HD-0-2816

Contractor : SRI International

Money Allocated: \$125,000 (FY 80); \$135,000 (FY 81)

Objectives: The purpose of this project is to synthesize the 19-nor-5 α -dihydrosteroids related to 5 α -dihydronortestosterone, 5 α -dihydronorprogesterone, and steroids having the Ring-A inverted half-chair conformation to maximize receptor binding and test as antiprogestational agents. These compounds will be tested for antifertility activity.

Major Findings: During the second contract year, four target compounds, two intermediates and two additional compounds have been prepared and tested, 17 α -ethynyl-17 β -hydroxy-5 α -estra-1(2)-en-3-one, pregna-4,9(11)-diene-3,20-dione, 9 α -fluoropregna-4,9(10)-diene-3,20-dione, 12 α -fluoro-pregna-4,9(11)-diene-3,20-dione, ethyl 2-(17 α -ethynyl-17 β -hydroxy-5 α -estran-2-yl) glyoxalate, 2-ethylidene-17 α -ethynyl-17 β -hydroxy-5 α -estran-3-one, 11 α -methoxyprogesterone. These compounds have been tested or are in the process of being tested for binding affinity to the progestin, estrogen and androgen cytosol receptor and submitted for evaluation for progestational or antiprogestational activities. The synthesis of the two remaining target compounds, 11 β -ethyl-19-norpregna-4,9(10)-diene-3,20-dione and 17 α -ethynyl-17 β -hydroxy-1 α ,11 α -(2-oxetano)-androst-4-ene-3-one is in progress. The key intermediate 20,20-ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10)-trien-11-one has been obtained and will be transferred to the 11 β -ethyl target compound. 17 α -Ethynyl-17 β -hydroxy-1 α ,11-(2-oxetano)-androsta-4,9(11)-diene-3-one has been synthesized and will be submitted to binding studies. The synthesis of its 9,11-dihydro analog is near its completion.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly relevant to the purposes of the Contraceptive Development Branch to support the synthesis and evaluation of novel steroidal compounds for contraceptive utility.

Proposed Course: The objectives of the contract were completed.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : C-18 Functionalized Steroids

Contract No. : N01-HD-0-2817

Contractor : State University of New York at Stony Brook

Money Allocated: \$86,968 (FY 80)

Objectives:

The purpose of this project is to synthesize a series of antagonists for the progestins as possible antifertility agents. By transferring the C-17 substituents to the C-18 methyl group, the compounds are hoped to be still bound to the receptors but unable to effect the subsequent biological events. These compounds will be tested for the antifertility activity.

Major Findings:

All of the proposed target compounds, 17-Deoxy-18-ethynyl-18-hydroxy-19-nortestosterone, 18-Acetyl-17-deoxy-19-nortestosterone, and 18-Acetoxy-18-acetyl-17-deoxy-19-nortestosterone, have been synthesized in 0.4 g quantities and tested as anti-progestational agents in the rabbit. None of these compounds showed significant antiprogestational activity. One of the 17-deoxy Ring A aromatic intermediates (3-methoxy-17-deoxy-18-hydroxyestra-1,3,5(10)-triene) was devoid of significant estrogenic activity when administered sc to rats at a dose of 1 mg total dose.

Significance to Biomedical Research and Program of the Institute:

The work undertaken in this project is directly relevant to the purpose of the Contraceptive Development Branch to support the synthesis and evaluation of novel steroidal compounds for contraceptive utility.

Proposed Course:

Termination in the absence of antiprogestational activity for these compounds.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Synthesis of Sulfur Analogs of Melatonin Derivatives

Contract No. : N01-HD-0-2818

Contractor : Indiana University

Money Allocated: \$28,887 (FY 80); \$28,477 (FY 81)

Objectives:

Two sulfur analogs of 6-substituted melatonin will be synthesized as an antiovu-
latory agent useful as a contraceptive agent.

Major Findings:

The multistep synthesis of 5-methoxy-6-chloro-3-(2¹-acetamidoethyl)benzo[b]thio-
phene has been accomplished, and the compound tested, and shown to have some ac-
tivity as an antiovu-
latory agent at a dose of 12 mg total dose in the rat. 5-Me-
thoxy-6-flouro-3-(2¹-acetamidoethyl)benzo[b]thiophene has recently been completed
and submitted for testing as an antiovu-
latory agent.

Significance to Biomedical Research and Program of the Institute:

The work undertaken in this project is directly relevant to the purposes of the
Contraceptive Development Branch to support the synthesis of specific nonsteroidal
compounds for evaluation for contraceptive utility.

Proposed Course:

The objectives of the contract were completed.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Synthesis and Testing of Functionalized Polymers as Potential
Contraceptive Agents
Contract No. : N01-HD-0-2819
Contractor : SRI International
Money Allocated: \$59,645 (FY 80)

Objectives: The objective of this project was to synthesize a water soluble functionalized polymer that can augment the barrier method of contraception. The hydrodynamic volume of the polymer would be such that the polymer would be non-absorbable across mucosal membranes and therefore systemically non-toxic. The polymer would consist of a polymer conjugate of a progestagen which would serve to inhibit spermatozoal action by interfering with plasma membrane function of the sperm.

Major Findings: A 5-carboxypentyl group was introduced onto norgestrel (1) at the 7α position to link the steroid to the polymer. This position was selected to minimize interaction of the tether and the polymer with the progestogen receptor site. A 15-step synthetic sequence was used to introduce this tether. The overall yield of 7α -(5-carboxypentyl)norgestrel (2) starting from 1 was 5%. Steroid 2 was converted in 68% yield to its p-nitrophenyl ester, which was then used to acylate poly(vinyl aminevinyl sulfonate sodium salt) (60:40). Ultraviolet and elemental analyses indicated that 20% of the polymer backbone amino groups were acylated by steroid, giving 0.78 mmol of steroid/g of polymer 3. Mass spectral analyses indicated that 0.06% (0.5 mol/g polymer) of the steroid, expressed as 7α -(5-carboxypentyl)norgestrel (2), was unbound. Unfortunately, a preliminary experiment indicated that steroid-polymer conjugate 3 had no effect on human spermatozoan forward migration.

Significance to Biomedical Research and the Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards development of new intravaginal contraceptives.

Proposed Course: Termination. All of the workscope objectives have been completed.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Synthesis of New Potent Oral Antigonadotropic Agents
for Male Fertility
Contract No. : N01-HD-O-2828
Contractor : SRI International
Money Allocated: \$119,048 (FY 80); \$128,383 (FY 81)

Objectives:

The goal of this contract is to synthesize new potent oral antigonadotropic androgenic agents for male fertility control. These compounds will be tested for the male contraceptive activity.

Major Findings:

Based on the biological leads eight compounds were selected for synthesis over a two year period; 6 α -fluoro-16 β -hydroxy-16 α -propyl-testosterone, 6 β -fluoro-16 β -hydroxy-16 α -propyl-testosterone, 2-cyano-16 α -propyl-5 α -estr-2-en-16 β , 17 β -diol, 2-cyano-7 α -methyl-5 α -estr-2-en-17 β -ol, 17 β -acetoxymethylene-17 α , 17 β -dihydroxy-D-homo-androst-4,14-diene-3-one 17-propionate, 16 β , 17 β -dihydroxy-2-methyl-16 α -propyl-5 α -estr-1-en-3-one, 16 β -hydroxy-7 α -methyl-16 α -propyl-19-nortestosterone, and 9 α -fluoro-16 β , 17 β -dihydroxy-16 α -propyl-androst-4,11-dien-3-one. The first five of the target compounds have been synthesized and the completion of the synthesis of the sixth is at hand. The first five target compounds and a number of synthetic intermediates were tested in the antigonadotropic and androgenic assays and none of them showed significant activity.

Significance to Biomedical Research and Program of the Institute:

The work undertaken in this project is directly relevant to the purpose of the Contraceptive Development Branch to support the synthesis and evaluation of novel steroidal compounds for contraceptive utility.

Proposed Course:

Termination in the absence of significant biological activity in these compounds.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Synthesis and Testing of Male Contraceptive Agents: Gossypol
Derivatives
Contract No. : N01-HD-0-2829
Contractor : SISA
Money Allocated: \$138,000 (FY 80); \$175,000 (FY 81)

Objectives: The purpose of this project is to investigate the structure-antifertility activity relationship in gossypol. The ultimate goal is the discovery of an effective male contraceptive which does not have the toxic properties of gossypol.

Major Findings: Structurally, gossypol is a dimer of hemigossypol which is a trihydroxydialkylnaphthaldehyde sesquiterpene. Targeted goals were set for the synthesis of (a) modified gossypol derivatives through manipulation of gossypol itself and (b) hemigossypol type structures via a total synthesis. As a result of work carried out to date at SISA Incorporated on this project, synthetic methods have been developed for selective modification in the gossypol structure itself to delineate the biological importance of various substituents in the gossypol molecule. Total synthesis of hemigossypol trimethyl ether has been achieved by two different routes. This has provided isomeric hemigossypol analogs and will allow further facile modification of the hemigossypol/gossypol nucleus. Ten compounds have been submitted to Mason Research Institute for antifertility screening in hamsters. In addition, thirty-six compounds were assayed in vitro for spermicidal activity by Dr. Anita Hoffer at Harvard Medical School under a subcontract since 9/81. Compounds tested in vivo showed no activity, but six compounds tested in vitro produced 100% inhibition of sperm motility in the spermicidal assay. Dr. Hoffer has also developed procedures for the examination of the ultrastructure of the testis, epididymis and epididymal sperm in hamsters made infertile with gossypol. Thus, a morphological baseline standard has been established against which new gossypol derivatives will be compared.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards the development of male contraceptive agents.

Proposed Course: This is expected to be a continuing contractual effort leading toward the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Peptide Inhibitors of LHRH as Ovulation Inhibitors

Contract No. : N01-HD-O-2830

Contractor : University of Louisville Foundation

Money Allocated: \$104,261 (FY 80); \$46,714 (FY 81)

Objectives: The objective of this project is to synthesize LHRH analogs that contain modified peptide backbone structures by replacement of amide bonds with thiomethylene [CH₂S] and its sulfoxide [CH₂SO], alkylthiomethylene [CHRS] and its sulfoxide [CHCH₃SO] and aminomethylene [CH₂NH]. These amide bond replacements might provide LHRH analogs with increased half lives of circulation and increased lipophilicity while maintaining conformational features necessary for receptor interaction.

Major Findings: Approximately 25 LH-RH related pseudopeptides have been prepared to date, representing modifications of both the parent LH-RH structure and various potent antagonists.

- a) The resulting activities are very much site-dependent; modifications of the 6-7 bond cause drastic loss in potency.
- b) Among antagonists, in vitro potencies approach those of parent peptides; in vivo results are much less than parent peptides in analogs prepared thus far.
- c) In general ψ [CH₂S] analogs are equal or superior to the corresponding sulfoxides ψ [CH₂SO].
- d) Thus far, ψ [CHCH₃S] analogs are the most promising candidates as sulfur-based amide bond replacements.
- e) In vivo potencies may be diminished partly as a result of increased lipophilicity of pseudopeptide antagonists.
- f) Pseudopeptides show significant in vivo activity when administered iv to immature female rats.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards development of new contraceptive agents.

Proposed Course: Termination. All of the workscope objectives have been accomplished.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Peptide Antagonists of LHRH as Ovulation Inhibitors
Contract No. : N01-HD-0-2831
Contractor : Tulane University School of Medicine
Money Allocated: \$171,283 (FY 80), \$183,225 (FY 81)

Objectives: The objective of this project is to prepare LHRH analogs modified in positions 1,2,3,6 and 10 to obtain more potent inhibitory activity. The analogs will be tested for in vivo and in vitro activity and receptor binding experiments will be conducted.

Major Findings: Previously to the present work, it was assumed that D-amino acids with large aromatic side-chains were required in position 6 of the LH-RH antagonists for the highest levels of biological activity to be reached. However, more recently it was discovered that (N-Ac-D-p-Cl-Phe^{1,2}, D-Trp³, D-Lys⁶, D-Ala¹⁰)-LH-RH was about twice as active as its D-Phe⁶-counterpart. Better still was the D-Arg⁶-analog which gave 78% blockade of ovulation at a 3 µg dose when dissolved in propylene glycol/saline and 40% blockade at a 750 ng dose in corn oil suspension form. Importantly, this new analog was quite soluble in water and in saline. The improved properties of these two peptides was clearly dependent on the degree of basicity of amino acid side-chain in the 6 position since D-amino acids with neutral, alkyl or acidic groups were much less effective. The desirability of having large lipophilic D-amino acids in position 1 was also demonstrated by the high activities of D-Trp¹-and, particularly, D-Nal¹-analogs. (N-Ac-D-p-Cl-Phe^{1,2}, D-Trp³, D-Arg⁶, D-Ala¹⁰)-LH-RH also exhibited oral activity in the rat. A 2 mg dose given by gavage resulted in complete blockade of ovulation and a 1 mg dose in about 80% blockade. These observations suggest that structural-oral activity studies with these potent new peptides are feasible.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards development of new contraceptive agents.

Proposed Course: This project will be continued under contract N01-HD-2-2809.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Peptide Antagonists of LHRH as Ovulation Inhibitors

Contract No. : N01-HD-O-2832

Contractor : University of Colorado Health Sciences Center

Money Allocated: \$176,746 (FY 80); \$165,864 (FY 81)

Objectives: The objective of this project is to design and synthesize antagonists of LHRH modified in such a manner as to increase receptor binding and improve resistance to enzymatic degradation.

Major Findings: The most potent compound, LRH-147, AcDTrp¹pClDPhe²DTrp³DArg⁶DAla¹⁰-LHRH inhibited ovulation completely at 6 µg (0/10). The receptor binding index of this compound was 0.92. The importance of the DAla¹⁰ substitution was assessed by testing AcpClDPhe^{1,2}DTrp³DArg⁶LHRH which led to partial inhibition of ovulation at 6 µg (2/9) and had a receptor binding index of 0.49. The DArg⁶ substitution with an AcAla or AcPhe in the 1 position and pClDPhe²DTrp³ without DAla at the 10 position led to inactive compounds at 6 µg (LRH 149, 7/11 at 6 µg; LRH 150, 11/11 at 6 µg). An AcDPhe¹ compound with the above substitutions was partially active (2/9 ovulated) at 6 µg. Advances in understanding the mechanism of action of LHRH antagonists were made. The antagonists acutely block the pituitary LHRH receptor leading to a rapid fall in serum LH and a delayed fall in serum FSH in castrate rats given a single injection of corn oil. The pituitary receptor blockade and inhibition of LH persist for 24 hours with a return to pretreatment values at 36 and 48 hours. The mechanism of the prolonged action of the LHRH antagonist is likely due to a combination of slowed dissociation rate from the receptor site compared to native LHRH and the continued delivery of antagonist from a corn oil depot into the circulation.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards development of new contraceptive agents.

Proposed Course: This project will continue under contract N01-HD-2-2812.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Peptide Antagonists of LHRH as Ovulation Inhibitors
Contract No. : N01-HD-0-2833
Contractor : University of Texas at Austin
Money Allocated: \$474,634 (FY 80)

Objectives: The objective of this project is to synthesize analogs of LHRH to produce antagonists with increased potency and duration of action.

Major Findings: Design, synthesis and assay of 84 analogs over two years resulted in increases in antagonist potency up to 12-fold. Selective refinement of substituents in positions 1, 2, 3, 6 and 10 provided the very potent antagonists. The most potent analog developed under this contract contained D-pyridyl-alanine substitutions in addition to D-Ala¹⁰. In the antioviulatory assay in the rat it is 100% inhibitory at 3 µg and 50% inhibitory at 1 µg. Two related analogs without the D-Ala¹⁰ substitution or with D-Trp instead of D-pyridyl-alanine were less active. The most novel analog synthesized during this time period [AcThr¹,DPhe²-DTrp^{3,6},DSer⁴,DTyr⁵,DArg⁸]-LH-RH contains 6 D-amino acid residues and 3 of them are at positions 4,5,8 where only occasionally have D-amino acid residues been substituted in other analogs. Although the potency of this analog was relatively weak, the inhibition of ovulation occurred at 25 µg (60%) and 12.5 µg (33%) with an IDR₅₀ of 1.3:1 in vitro (pituitary cell culture assay). In principle this appeared to be an important new type of analog because the "hexa-D analog" was less likely to be biologically degraded and could give leads to analogs with increased oral activity. Finally, non-correlative observations between in vitro (pituitary cell culture) and antioviulatory results may reflect differences in absorption of the analogs from the sc injection site and may indicate that differences in absorption may be a major determinant of the in vivo potency of the analog.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards development of new contraceptive agents.

Proposed Course: This project will be continued under contract N01-HD-2-2810.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Peptide Antagonists of LHRH as Ovulation Inhibitors

Contract No. : N01-HD-0-2836

Contractor : Salk Institute

Money Allocated: \$401,538 (FY 80)

Objectives: The objective of this project is to improve the potency of presently available LHRH antagonists by designing and synthesizing analogs based upon Hansch analysis as modified by Topliss. The premise is that improved potency of existing antagonists can be achieved if the predominant factors (hydrophobicity, electronic distribution or steric factors) affecting the antagonist's efficacy can be identified for loci which contain aromatic side chains.

Major Findings: Thirty-five LHRH antagonists were synthesized. Two new analogs were developed that are about three times more potent than the best analog reported a year ago; these analogs have the added advantage of being slightly more soluble in aqueous solutions. What is perhaps most significant is the demonstration that several parameters determining conformational, as well as those responsible for hydrophobic/hydrophilic or electronic effects, are very important and do not have to be necessarily located at one particular position in the LHRH sequence even though they may be very spatially close in the active conformers. This is best illustrated by the fact that very hydrophobic residues at the 6 position are compatible with some fairly hydrophilic substituents at the N-terminus, i.e. [Ac- Δ^3 Pro¹, 4FDPhe², D2NAL^{3,6}]-LHRH (100% active subcutaneously at 2.5 μ g/rat), while a very hydrophilic residue such as DArg⁶ also gives a very potent analog as long as the N-termini becomes more hydrophobic (100% active at < 1 μ g/rat). Oral antioviulatory activity was demonstrated for one of the most potent LHRH antagonists.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards development of new contraceptive agents.

Proposed Course: This project will be continued under contract N01-HD-2-2807.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Isolation and Purification of Rat Androgen Binding Protein

Contract No. : NO1-HD-O-2845

Contractor : Population Council

Money Allocated: \$106,671 (FY 80); \$91,912 (FY 81); \$48,460 (FY 82)

Objectives: To produce 100 radioimmunoassay (RIA) kits for the quantification of rat androgen binding protein (ABP). This goal is to be implemented by the purification of ABP and generation of antibodies against it, and development of an RIA using these reagents. The goals for the first year include the preparation of the immunogen, immunization of rabbits, collection of antisera and preparation of the tracer ABP.

Major Findings: All the materials needed to assemble the 100 kits for an RIA of rat ABP have been collected. In addition, they have been tested by several independent laboratories and have been shown to function properly. However, a few problem areas have surfaced; the labs felt that the ion exchange chromatography step utilized to clean up the iodinated ABP presented some difficulty. As a result a simpler means of cleaning up the tracer to replace the DEAE gradient eluted chromatography step is being sought.

The possibility of using only a single concentration of salt rather than a gradient to elute the immunoreactive tracer from the DEAE column had previously been evaluated and proved to be unsatisfactory. Since the charge difference between the damaged and undamaged tracer was very little, they were not adequately resolved. Since then, a change was made in the procedure for iodination from a chloramine T/metabisulfite reaction to the more gentle "Iodogen" method. Therefore, the possibility of a single step elution protocol is being re-examined.

Two problems have arisen with regard to preparing the tracer and displacement standard in a form that is convenient for shipping. During lyophilization there is an increased amount of ABP aggregation, resulting in a loss in excess of 50% of label to work with. The resulting labeled tracer, which is not aggregated, seems to retain its immunoactivity since it binds to the antibody and is displaceable by cold ABP. This binding and displaceability is not as good as for ABP stored frozen in glycerol. Attempts are being made to either deaggregate the labeled ABP or perhaps prevent it from happening in the first place.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards development of the new male methods of contraception.

Proposed Course: This is expected to be a continuing contractual effort leading toward the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Development of Microcapsules Containing a Contraceptive Progestagen
Contract No. : N01-HD-O-2847
Contractor : Biotek, Inc.
Money Allocated: \$166,711 (FY 80); \$109,228 (FY 81)

Objectives: The objective of this program is to develop and test an injectable microcapsule system for the delivery of the synthetic contraceptive progestagen, levonorgestrel. The drug is encapsulated in spherical biodegradable polylactide polymer reservoirs which deliver the hormone over a period of six months.

Major Findings: During the current fiscal period, the biodegradable poly-L(-)lactide prepared earlier was characterized. The residual monomer, residual solvent, and leachable tin content were analyzed and found to be present at insignificant levels and/or within acceptable limits.

A total of nine microencapsulation runs were made using the air suspension coating process. The microcapsules were characterized by size distribution, hormone content, scanning electron microscopy, and in vitro rate of drug release. The in vivo rate was also evaluated in a few batches by following the blood level of the drug in rabbits. These data were obtained by the Contraceptive Development Branch at its biological testing facility. The aim of the runs was to optimize the microencapsulation process, and to evaluate its ability to prepare the target microcapsules reproducibly, at high enough yields.

The results to date indicate that this has been accomplished: the 105-150 μm microcapsules delivered the target dose in vitro and produced a good dose response in rabbits. Three batches which were prepared under identical conditions to evaluate reproducibility showed similar drug release profiles. In preparation for IND application to the FDA, Standard Operating Procedures related both to the general operation and specifically to this project have been completed. A Drug Master File is in final review.

Significance to Biomedical Research and the Program of the Institute: Development of new contraceptive technology is a stated goal of the Contraceptive Development Branch.

Proposed Course: This project is expected to be a continuing contractual effort leading to the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Development of Hydrogel Materials as Vaginal Barrier
Contraceptives
Contract No. : N01-HD-0-2854
Contractor : Southern Research Institute
Money Allocated: \$546,338 for 3 years (FY 80)

Objectives: The objective of the project is the development of spermicide-releasing hydrogel materials for use as disposable (single-use) vaginal barrier diaphragms.

Major Findings: During the past year, the hydrogel materials were evaluated thoroughly for use in the fabrication of vaginal diaphragms. Despite considerable effort to improve their mechanical strength, both the poly(hydroxyalkyl methacrylates) and poly[dodecamethylene-3,3-bis(hydroxymethyl)glutaramides] (Nylon 5-0-12) proved to be unacceptable for use as diaphragm materials.

Estane 5714F-1, a polyether-polyurethane, was evaluated as a candidate material and found to have mechanical properties superior to commercial diaphragms. Estane was loaded with nonoxynol-9 (NN9) spermicide and evaluated for in vitro NN9 release and mechanical properties. Estane film loaded with 10 wt % NN9 gave the approximate target release, but did not release NN9 fast enough initially. Several methods of producing an initial "burst" of NN9 from Estane were investigated, and it was discovered that the addition of 15% polymer weight of polyethylene glycol, 1540 mol wt (PEG-1540), to the 10% NN9/Estane blend resulted in the desired release of NN9 from Estane.

Prototype baboon diaphragms of several sizes were fabricated by a dipcasting technique and evaluated for in vivo fit and retention. The proper size was determined, and diaphragms of several NN9/PEG-1540/Estane combinations were fabricated and evaluated for in vitro NN9 release. Diaphragms 40 mm in diameter and composed of 9% NN9/15% PEG-1540/Estane gave the target release of spermicide for baboons. The mechanical properties of this material are adequate when cast and superior when thermally processed to commercial diaphragm materials. A method of diaphragm fabrication based on thermal processing is currently being developed.

The in vitro spermicidal testing of NN9/PEG-1540/Estane diaphragms by the Sander-Cramer test has been completed. Vaginal irritation and efficacy studies in baboons are currently in progress. Prototype rabbit diaphragms have been fabricated and are being tested for in vivo fit and retention.

Significance to Biomedical Research Program of the Institute: Development of new contraceptive technology is a stated goal of the Contraceptive Development Branch.

Proposed Course: This is expected to be a continuing contractual effort leading to the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Development and Testing of a New Cervical Cap and Inserter

Contract No. : N01-HD-O-2855

Contractor : Brigham and Women's Hospital

Money Allocated: \$428,649 (FY 80 for 2 years)

Objectives: The goal of this project is to develop an improved contraceptive cervical cap.

Major Findings: It is desired to produce new and improved contraceptive cervical caps that will be easy to use, at least as effective as intrauterine devices and available in a range of sizes and shapes large enough to accomodate at least 95% of women of fertile age. In pursuing this goal the initial efforts were largely met with frustration and failure. An important intermediate objective which was to survey the sizes and shapes of women's cervices by making and measuring impressions and casts of a representative sample of the fertile population, had to be abandoned. The cervical surface proved so compliant that every method of impression taking caused changes in the cervix that could neither be controlled nor duplicated. However, an appreciation of the remarkable changeability of the cervix was acquired and this knowledge has been indispensable to the more recent work described below.

Hypotheses about successful cap design have been based on the analysis of semi-successful caps. New designs and prototypes capitalizing on successful mechanisms were made and tested and improved. An application for Investigational Device Exemption was submitted to the FDA, and has now been approved. A method for objectively measuring cap retention force has been under development. Relatively quick and inexpensive molding techniques have been developed and new caps have been fabricated for testing. The first experimental caps have recently been placed in women in whom other caps have not been retained effectively and no dislodgements have so far occurred.

Significance to Biomedical Research Program of the Institute: Development of new contraceptive technology is a stated goal of the Contraceptive Development Branch.

Proposed Course: This project is expected to be a continuing contractual effort leading to the development of improved contraceptive technology.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Isolation, Characterization and Synthesis of Gonadocrinin
Contract No. : N01-HD-0-2860
Contractor : The Salk Institute
Money Allocated: \$402,719 (FY 80)

Objectives: A new polypeptide of ovarian origin that possesses the characteristics of LRF, although of different chemical structure, has been discovered. It very well may represent an internal regulator of ovarian function, as well as participating in the overall hypothalamic-pituitary-ovarian interrelation. The objective of the proposal is to isolate, purify and characterize the LRF-like material, gonadocrinin, from rat ovaries, establish the primary molecular structure of the substance, reproduce it by total synthesis, develop a RIA for the peptide, and demonstrate that the native and synthetic materials are biologically active. RIA reagents will be provided to NIH for distribution to other investigators.

Major Findings: Isolation of gonadocrinin an ovarian peptide with LRF like activity from PMSG stimulated rat ovaries has been terminated because of inconclusive results. Material isolated from the ovaries had the HPLC behavior as one of the synthetic superagonists or behaved as native LRF. The quantity that could be isolated varied from batch to batch of the ovaries. It is possible that the material is of endogenous origin and corresponds to native LRF or behaves as native LRF in the chromatographic systems employed to date. On the other hand it may indeed represent contamination of the ovarian extracts in the laboratory. Attempts are being made to look for this material in porcine follicular fluid.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards development of new contraceptive drugs.

Proposed Course: Since isolation of gonadocrinin from rat ovaries could not be accomplished. The contractor is attempting to isolate it from porcine follicular fluid. If unsuccessful the contract will be terminated.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Development and Testing of Vaginal Contraceptives

Contract No. : N01-HD-1-2800

Contractor : International Fertility Research Program

Money Allocated: \$643,771 (FY 81)

Objectives: It is proposed to carry out a multi-clinic Phase III clinical trial of a newly developed non-prescription vaginal contraceptive method, the Secure Sponge, in comparison with the diaphragm with spermicide. The incidence of adverse side effects and complaints associated with the use of the Secure sponge compared with the diaphragm will be evaluated. Further, the rates of user compliance for the Secure sponge will be determined. The sponge affords several significant advantages over the diaphragm. First, a single size can be used by all women; second, it is intended to be a non-prescription contraceptive; third, it is less messy than other contraceptives and can be inserted up to 24 hours in advance of coitus.

Major Findings: In March 1982, the one year recruitment phase was completed. More than 1450 subjects were recruited into the trial at 13 clinics across the U.S.. The one year follow-up phase is ongoing. The trial has progressed very smoothly. There were some problems reported at the start with regards to sponges tearing upon removal. However, these appear to have been solved by a modification of the sponge.

Data received at the IFRP show a small difference in the performance rate of the two study methods, with the diaphragm performing somewhat better. This difference, however, disappears when data from subjects who were vaginal contraceptive users at the time of entry into the study, but had been assigned to the diaphragm group through random allocation, are deleted from the analyses. Among women who were not using a vaginal contraceptive at the time of entry into the study, there were no significant differences in the performance rates for the two methods. Additional follow-up is needed before results can be considered conclusive. The clinics, however, continue to report the enthusiasm and support that sponge users express about the future of the contraceptive sponge.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards development of the new female methods of contraception.

Proposed Course: This is expected to be a continuing contractual effort leading toward the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Development and Testing of Vaginal Barrier Contraceptives

Contract No. : N01-HD-1-2801

Contractor : International Fertility Research Program

Money Allocated: \$171,333 (FY 81 for 18 months)

Objectives: To test a custom-fit cervical cap with a one-way valve which allows discharge from the cervix for up to six months in 300 women in order to determine preliminary estimates of safety, efficacy and acceptability.

Major Findings: The International Fertility Research Program (IFRP) was awarded a contract to conduct a multiclinic Phase II trial of a custom valved cervical cap (Contracep).

Studies were initiated at each of three clinics with the developers of the Contracep, who serve as IFRP consultants in the trial, conducting training sessions for pertinent clinic personnel at each of the three sites. The studies were phased in and the first, at Planned Parenthood of Milwaukee, was initiated in September 1981, the second, at Planned Parenthood-World Population of Los Angeles, in December 1981, and the third, at Mt. Sinai in New York City, in February 1982.

After reports of cap dislodgements, which may have resulted from problems with the impression-taking material, and confirmed pregnancies, the recruitment of additional subjects into the trial was halted. Reports of additional confirmed pregnancies caused NICHD, with IFRP concurrence, to terminate the trial and request that all caps, including those successfully used, be returned to the clinics and forwarded to IFRP.

Revisions to the study, should it be restarted, have been proposed to and approved by the IFRP's Institutional Review Board (IRB), namely changing the impression-taking material from alginate to silicone and having all volunteers use an adjunctive contraceptive during the first month of cap use. It is thought that dislodgements, if they occur, will occur in the first weeks of cap use.

Significance to Biomedical Research and Program of the Institute: Development of new contraceptive methods is a stated goal of the Contraceptive Development Branch.

Proposed Course: The clinical evaluation of the Contracep may be restarted if Contracep, Inc. obtains Food and Drug Administration (FDA) approval for use of the new impression material, and if Contracep can provide data to NICHD and the IFRP to demonstrate the effectiveness of any modified cap and/or fitting procedures.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Use-Effectiveness Study of Cervical Caps

Contract No. : N01-HD-1-2804

Contractor : Los Angeles Regional Family Planning Council, Inc.

Money Allocated: \$477,303 (FY 81); \$650,385 (FY 82); \$599,267 (FY 83);
\$389,040 (FY 84)

Objectives: The purpose of the proposed research is to evaluate the contraceptive effectiveness of the cervical cap, its side effects, and how well it will be accepted by different segments of the population. This will be a multi-center, prospective clinical study in which the cap will be compared to the vaginal diaphragm. It will be conducted under the auspices of a group of investigators associated with the Los Angeles Regional Family Planning Council, which will coordinate and monitor the project as well as provide for the analysis and interpretation of the data collected. The data should be sufficient to predict whether or not the cap will be a useful addition of the contraceptive methods presently in use throughout the country.

Major Findings: During the period 8/1/81 to 5/31/82 the organization of the multi-center clinical study of the efficacy of cervical caps was organized and the initial phase of the preliminary clinical study, conducted to assess side effects of the Cavity Rim and Vimule Caps, was completed. It was found that the Vimules caused lesions of the portio vaginalis ranging from erythematous impressions to abrasions and frank lacerations. Lesions were related to cap size and duration of wear. Disruption of the vaginal epithelium occurred in 8 of 12 subjects and it was elected to discontinue using this device. The development of malodor was also evaluated and found to be related to length of wear. A large proportion of women developed malodor after wearing a cap for 7 or 5 days (67% and 60% respectfully), but fewer than 10% had this problem when caps were worn for three days or less. Three days was selected as the recommended period of wear in the efficacy study.

In preparation for the clinical trials, the first six months were spent developing and testing data collection forms, and preparing training manuals and patient education materials. Recruitment and training of additional research staff members, and four nurse clinicians for the field clinics, was completed. After receiving final FDA and IRB approval, volunteer recruitment was initiated in several of the field sites and over 125 patients have been enrolled into the study to date.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards development of the new female methods of contraception.

Proposed Course: This is expected to be a continuing contractual effort leading toward the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Synthesis and Testing of Novel Steroids as Antiprogestational Agents
Contract No. : N01-HD-1-2807
Contractor : Research Triangle Institute
Money Allocated: \$114,554 (FY 81); \$152,039 (FY 82)

Objectives:

The purpose of this project is to synthesize retrotestosterone derivatives and 16-ethynyl derivatives of testosterone as antiprogestational agents. These compounds will be tested for antifertility activity.

Major Findings:

As anticipated, the reaction of lithium dimethylcuprate with 6-dehydroretrotestosterone gave after isomerization exclusively the 7 β -methyl isomer. The stereochemistry of the methyl group at C-7 was determined by x-ray crystallography. Sodium borohydride reduction of 7 β -methyl-9 β ,10 α -androst-5-en-17 β -ol-3-one gave the corresponding 3 α -hydroxy compound. Reduction of 7 β -methylretrotestosterone with lithium and ammonia gave the 5 β -isomer whereas catalytic hydrogenation of the same yielded 5 α -isomer. The synthesis of the 7 α -methyl derivatives of retrotestosterone is in progress. The above seven retrosteroids and retroprogesterone were tested for in vitro binding to the cytosol progesterone receptor of the estrogen primed immature rabbit uterus. Retroprogesterone exhibited the greatest binding of all the compounds tested. The remaining seven compounds possessed considerably less binding affinity for the progesterone receptor than retroprogesterone.

Significance to Biomedical Research and Program of the Institute:

The work undertaken in this project is directly relevant to the purposes of the Contraceptive Development Branch to support the synthesis and evaluation of novel steroidal compounds for contraceptive utility.

Proposed Course:

This is expected to be a continuing contractual effort leading toward the development of new chemical contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Synthesis and Testing of Antiprogestational Agents

Contract No. : N01-HD-1-2808
Contractor : Research Triangle Institute
Money Allocated: \$107,421 (FY 81)

Objectives:

The purpose of this project is to synthesize progesterone derivatives such as 17α -substituted 19-nor- 5α -pregnane-3,20-dione, 17α -substituted- 5α -pregnandione, 17α -substituted 19-norprogesterone and 17α -substituted progesterone. The structural features exhibited by these compounds may be expected to impart affinity for uterine progesterone receptor sites, and to possess antiprogestational activity. These compounds will be tested for antifertility activity.

Major Findings:

The 17α -anion of pregnenolone is readily available by treatment of the enol acetate with methyl lithium. Reaction of the anion with formaldehyde gave the known 17α -hydroxymethylpregnenolone, which was oxidized by pyridinium chlorochromate to 17α -formylprogestosterone. O,O-Dimethyldiazomethylphosphonate/potassium *t*-butoxide reacts with high selectivity (possibly specifically) with the formyl group to give 17α -ethynylprogesterone directly in good yield. This compound can thus be prepared in four steps and acceptable overall yield from the readily available pregnenolone acetate. Furthermore, the way is now open to the synthesis of 19-nor and 5α -dihydro analogs, as well as other analogous compounds.

Significance to Biomedical Research and Program of the Institute:

The work undertaken in this project is directly relevant to the purposes of the Contraceptive Development Branch to support synthesis and evaluation of novel steroidal compounds for contraceptive utility.

Proposed Course:

This is expected to be a continuing contractual effort leading toward the development of new chemical contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Synthesis and Testing of Antiprogestational Agents
Contract No. : N01-HD-1-2809
Contractor : SRI International
Money Allocated: \$164,747 (FY 81) \$178,422 (FY 82)

Objectives: The objective of this project is to synthesize 15,16-seco analogs possessing a ring A inverted half-chair form that promotes optimal receptor binding in accord with a ring A-initiated binding model and/or that are conformationally similar to 5 α -dihydroneorethindrone, a reported in vivo antiprogestational agent.

Major Findings: The synthesis of seco compounds 17 ϵ -acetoxy-15,16-seco-19-norandrosta-4-en-3-one, 17 ϵ -acetoxy-15,16-seco-19-norandrosta-4,6-dien-3-one, 17 ϵ -acetoxy-7 α -methyl-15,16-seco-19-norandrosta-4-en-3-one and 7 α -methyl-15,16-seco-19-norandrosta-4-en-3-one and 7 α -methyl-15,16-seco-19-norandrosta-4-en-3,17-dione have been completed. These seco derivatives have shown significant relative binding affinity for the progesterone receptor. Additional in vitro cytosol binding studies (estrogen and androgen) have also been conducted. The in vivo progestational and antifertility assays are in progress.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards development of new contraceptive agents.

Proposed Course: This is expected to be a continuing contractual effort leading toward the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Synthesis and Testing of Antiprogestational Agents

Contract No. : N01-HD-1-2810

Contractor : The Research Foundation of the State University of New York

Money Allocated: \$55,698 (FY 81); \$22,465 (FY 82)

Objectives: The purpose of this project is to synthesize tetracyclic compounds possessing a displaced C ring steroids (when compared to natural steroids) to maximize binding to the progesterone receptor as well as to maintain the compound's stereochemical integrity of the major functions of the B and C rings of natural steroids. These compounds will be tested for antiprogestational activity as well as for antifertility activity.

Major Findings: Following the proposed synthetic procedure, the compound thus obtained was found to be the corresponding C-17 isomer of $7\beta,15\alpha$ -ethano-11,12-seco-11,19-bisnorpregn-4-ene-3,20-dione according to X-ray crystallography. As a result, the final stages of the synthesis were modified to produce a compound of opposite stereochemistry. The unexpected difficulties encountered during the course of the synthesis of the corresponding D-homo compounds will also delay substantially to prepare all target compounds within the original 16 month contract period. Many blocking groups which have been used successfully in analogous situations were tried with little success. Therefore, a better method to cleave the blocked intermediate used in the synthesis of $7\beta,15\alpha$ -ethano-11,12-seco-11,19-bisnorpregn-4-ene-3,20-dione to an α -diketone has been developed. It is hoped that this α -diketone can readily be converted to the substituted cyclohexanone required for the corresponding D-homo series.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly relevant to the purposes of the Contraceptive Development Branch to support the synthesis and evaluation of novel steroidal compounds for contraceptive utility.

Proposed Course: The objectives of the contract will be completed.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Synthetic Chemical Facility
Contract No. : N01-HD-1-2811
Contractor : Southwest Foundation for Research and Education
Money Allocated: \$240,716 (FY 81); \$259,973 (FY 82); \$280,770 (FY 83); \$303,230 (FY 84); \$327,490 (FY 85)

Objectives: The purpose of this project is to have this synthetic chemical facility synthesize rapidly laboratory scale as well as larger quantities of specific compounds required by the Contraceptive Development Branch for contraceptive investigation.

Major Findings: During the first year of the contract a total of twenty compounds have been synthesized, including multistep syntheses of unnatural amino acids and modified steroids on the 100 gram scale. Preparation of 68 g of 3-(2-naphthyl)-D-alanine beginning with 350 grams of 2-(bromoethyl)naphthalene has been completed. 2-Pyridyl-D-alanine (25 g) and a 4-Pyridyl-D-alanine (25 g) were prepared starting from the corresponding picolyl chloride hydrochloride. A number of long acting esters of levonorgestrel in sufficient quantities were prepared including formate, butyrate and isobutyrate as well as their oxime derivatives. 7 α -Methyl-norethindrone was synthesized from 100 grams of 7 α -methyleneestrone in seven steps. A number of ester and oxime derivatives were also prepared and tested as long acting progestins. (-)-6 α -Methylnorgestrel was prepared in eight steps from (+)-13 β -ethyl-17 β -hydroxygon-4-en-3-one. (-)-7 α -Methylnorgestrel was also prepared in ten steps from the same intermediate, (+)-13 β -ethyl-17 β -hydroxygon-4-en-3-one. The cyclobutylcarboxylate ester and oxime derivatives were prepared. None of the esters and oximes prepared from (-)-6 α - and 7 α -methylnorgestrel demonstrated long acting contraceptive properties. 7 α -Methyleneestrone (100 gr) was converted to 7 α -methyl-14-dehydro-19-nortestosterone in ten steps as a potent androgen. Synthesis of 16-fluoro-13-dehydro-prostaglandin F_{2 α} was begun with 3 kg of 2-bromohexanoic acid. The many problems encountered in the multistep, large scale procedure have been successfully resolved and eight of the eleven steps have been utilized for separation and purification of various intermediates. It is hoped that the synthesis of the final compound will be completed soon and available for evaluation for luteolytic activity in the monkey.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly relevant to the purposes of the Contraceptive Development Branch to support the synthesis of specific steroidal and nonsteroidal compounds for evaluation for contraceptive utility.

Proposed Course: This is expected to be a continuing effort leading toward the development of new chemical contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : The Development and Testing of New Spermicides

Contract No. : N01-HD-1-2828

Contractor : Syntex Research Division

Money Allocated: \$457,819 (FY-81), \$369,215 (FY-82), \$120,939 (FY-83)

Objectives: The aim of the program is to develop and test a new spermicidal contraceptive based on a 1-substituted imidazole (RS-37367). Besides having greater spermicidal potency than presently available surfactant materials, the new compound may have certain unique properties. It appears to bind to sperm, enter cervical mucus more readily and prematurely triggers an acrosome-like reaction in sperm. A prototype gel-formulation is also proposed to satisfy esthetic criteria and offer superior properties with regard to mixing of the spermicide with ejaculate and enhancing its delivery to the cervical mucus.

Major Findings: Preclinical evaluation of RS-37367 has been proceeding. The compound, as oxalate salt formulated in a gel, shows good efficacy for 12 to 16 hours after insertion in the stump-tailed macaque, postcoital assay judged by sperm recovered in cervical mucus. An HPLC assay has been developed and used to demonstrate the presence of spermicidal quantities of RS-37367 in this cervical mucus. Scanning electron microscopy of human cervical mucus exposed to RS-37367 in vitro for a little as 5 minutes reveals ultrastructural changes in the mucus which would be expected to act as a physical barrier to sperm penetration. These in vitro findings could explain some of the in vivo results in monkeys.

Preformulation work indicated RS-37367 to be chemically stable in the gel formulation for at least 19 months, although the fact that the oxalate salt was poorly soluble and was a supersaturated solution at 1% in the gel was a cause of some concern. This was overshadowed by the findings of deposition of crystalline material within the vaginal tissue following a 10 day vaginal tolerance test in rabbits using the oxalate salt but not the hydrochloride or free base. Emphasis is presently upon the identification of a bioefficacious and biocompatible alternative salt form. Preliminary data suggest this to be a feasible objective.

Radiolabelled RS-37367 (^3H and ^{14}C) has been synthesized and tissue distribution studies in rats have begun. Pharmacological characterization of the compound gives no cause for concern.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards development of the new female methods of contraception.

Proposed Course: This is expected to be a continuing contractual effort leading toward the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Development and Testing of New Spermicides

Contract No. : N01-HD-1-2829

Contractor : Biotek, Inc.

Money Allocated: \$91,559 (FY 81); \$85,264 (FY 82)

Objectives: The objective of this program is to develop a composite bioerodible spermicide suppository which melts at 36-37°C and which delivers an initial effective dose of nonoxynol-9 spermicide after one minute and continues to deliver a controlled dose of spermicide for a period of 16 hours. The composite suppository is composed of two spermicidal formulations: a fast-melting water-soluble foaming suppository and a bioerodible water soluble spermicide film which is imbedded in the body of the suppository.

Major Findings: Polyvinyl alcohol polymers were chosen for developing the bioerodible water soluble spermicide film. Films were prepared and tested for the release of nonoxynol-9 and the results correlated with the degree of hydrolysis of the polymer, polymer molecular weight, film thickness, spermicide loading, heat treatment, boration, and the effect of plasticizers. The results showed that the following treatments reduce the rate of spermicide release from the films: increasing the level of polymer hydrolysis, increasing film thickness, reducing spermicide loading and heat treatment. Alternately, the following treatments increase the rate of spermicide release: reducing the level of polymer hydrolysis, reducing film thickness, increasing spermicide loading, and boration.

An effervescent suppository was developed with the desired characteristics. Sodium bicarbonate and citric acid were used as effervescent ingredients. Several test methods were developed to test the physical and chemical integrity of the finished formula. These tests were pH, hardness, disintegration time, melting range, sedimentation, and weight variation. Content uniformity of nonoxynol-9 in the suppository was evaluated and an assay method for total drug content in the suppositories was also tested.

Significance to Biomedical Research and the Program of the Institute: Development of new contraceptive technology is a stated goal of the Contraceptive Development Branch.

Proposed Course: This project is expected to be a continuing contractual effort leading to the development of a new contraceptive and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Peptide Antagonists of LHRH as Gonadotropin Inhibitors

Contract No. : N01-HD-2-2807
Contractor : Salk Institute
Money Allocated: \$306,015 (FY 82)

Objectives: The objective of this project is to optimize the hydrophobic/hydrophilic character of LHRH antagonists while increasing potency. The goals of increased potency (s.c. and p.o.) and duration will be approached in a systematic medicinal chemical manner. The focus is on variation of substituents on aromatic side chains. Molecular dynamics will be used in the design and synthesis of more potent LHRH antagonists. The antagonists will be assayed by in vitro and in vivo methods.

Major Findings: This project has only recently begun and there are no results to report at this time.

Significance to Biomedical Research and Program of The Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards the development of male contraceptive agents.

Proposed Course: This is expected to be a continuing contractual effort leading toward the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Peptide Antagonists of LHRH as Gonadotropin Inhibitors

Contract No. : N01-HD-2-2808
Contractor : Indiana University Foundation
Money Allocated: \$99,014 (FY 82)

Objectives: The objective of this project is to incorporate α -methyl amino acid substituents into the currently available most potent LHRH antagonists in view of their known conformational effects. There are several methods of increasing apparent activity. One is by increasing affinity which can be accomplished by increased complementarity of peptide to receptor or by decreased entropy if the analogs solution conformer can be "frozen" close to that required for binding. The α -methyl analog will take advantage of both of these approaches. The antagonists will be sent to the Contraceptive Development Branch for testing.

Major Findings: This project has only recently begun and there are no results to report at this time.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards the development of male contraceptive agents.

Proposed Course: This is expected to be a continuing contractual effort leading toward the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Peptide Antagonists of LHRH as Gonadotropin Inhibitors

Contract No. : N01-HD-2-2809
Contractor : Tulane University
Money Allocated: \$212,940 (FY 82)

Objectives: The objective of this project is to examine single amino acid substituents in the prototype antagonist [Ac-D-p-CI-Phe^{1,2},D-Trp³,D-Ar⁶,D-Ala¹⁰]LHRH, which is the most potent analog to date. The major emphasis is on an extensive investigation of position six in order to optimize the relative merits of aromatic and/or basic substitutions. Unnatural basic amino acids will also be incorporated with position one and a reinvestigation of position three in combination with D-Arg⁶ will be made. In vitro and in vivo biological evaluation of these analogs will be performed.

Major Findings: This project has only recently begun and there are no results to report at this time.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards the development of male contraceptive agents.

Proposed Course: This is expected to be a continuing contractual effort leading toward the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Peptide Antagonists of LHRH as Gonadotropin Inhibitors

Contract No. : N01-HD-2-2810

Contractor : University of Texas at Austin

Money Allocated: \$241,450 (FY 82)

Objectives: The objective of this project is to synthesize LHRH antagonists with increased potency (s.c. and p.o.) and duration of action. Top priority will be given to increasing potency through systematic variations in position 1 of LHRH for current most potent antagonists including D-Arg⁶. Heteroaromatic substitutions will be tried in positions 3 and 6. Two approaches to increased duration will include multi-D substitutions (positions 1, 2, 3, 4, 5, 6, 8). These analogs will be tested in vitro and in vivo.

Major Findings: This project has only recently begun and there are no results to report at this time.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards the development of male contraceptive agents.

Proposed Course: This is expected to be a continuing contractual effort leading toward the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Development Branch
Contract and Collaborative Research

Contract Title : Peptide Antagonists of LHRH as Gonadotropin Inhibitors

Contract No. : N01-HD-2-2812

Contractor : University of Colorado Health Sciences Center

Money Allocated: \$159,201 (FY 82)

Objectives: The objective of this project is to synthesize LHRH antagonists substituted with various charged and polar unusual amino acids, including substituted aromatics in order to probe questions of hydrophobicity versus hydrophilicity. The biological potency of these analogs will be determined by in vitro and in vivo assays.

Major Findings: This project has only recently begun and there are no results to report at this time.

Significance to Biomedical Research and Program of the Institute: The work undertaken in this project is directly related to the published purpose of the Contraceptive Development Branch to support research directed towards the development of male contraceptive agents.

Proposed Course: This is expected to be a continuing contractual effort leading toward the development of new contraceptives and is an integral part of the contraceptive development program.

NICHD ANNUAL REPORT

October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Center for Population Research

The Contraceptive Evaluation Branch is responsible for a comprehensive research contracts program on the evaluation of the safety and effectiveness of methods of contraception and fertility regulation that are in use throughout the United States. Surveillance for adverse health effects, quantification of the medical risks, and understanding the important underlying pathophysiological mechanisms in the user population serve as the major charge of the Branch. In addition, the Branch evaluates the effectiveness of all methods of contraception and determines additional health benefits subsequent to the use of contraception and fertility regulation. Major program components deal with these issues in users of steroid contraceptives, intrauterine devices, male sterilization, and barrier methods.

Steroid Contraceptives

The overall program goal in steroid contraceptives is to determine frequencies of major health effects and minor side effects associated with oral contraceptive use, to elucidate causation and pathogenesis of these medical effects, and to develop measures and methods for prevention and therapy of those clinical entities that comprise the medical effects of oral contraceptives. In fiscal year 1982, there were three active components of the steroid contraceptive research program. These include: (1) Steroid Contraceptives and Cardiovascular Disease, (2) Steroid Contraceptives and Neoplasia, and (3) Steroid Contraceptives and Diabetes Mellitus.

A major study has been underway to evaluate the effects of three currently marketed oral contraceptive (OC) formulations on lipoprotein patterns, glucose tolerance, and insulin secretion in women. It is believed that data from this study will indicate whether or not some oral contraceptive formulations may increase the risk of cardiovascular disease by accelerating the process of atherogenesis, e.g., by decreasing high density lipoprotein cholesterol, decreasing glucose tolerance, etc. During the fiscal year 1982, women 18-30 years of age who initiated oral contraceptive use were randomly assigned to one of three oral contraceptive formulations. Progress was also made in recruiting a control group of 100 women not using OCs at all. On all studied women, blood specimens, medical histories, and 24 hour dietary recalls are being obtained.

Two contracts proceeded towards closure on the presence of abnormal proteins in the serum of oral contraceptive users. The purpose of these projects is to confirm and extend the work of Beaumont et al. on an abnormally precipitating globulin (GAP) found in the serum of some women using OCs. Such a finding would indicate that a derangement of protein metabolism might be involved in the development of thrombotic disease in users of oral contraceptives. Preliminary analyses of data, however, do not seem to confirm Beaumont's finding. Contracts pending final award in the steroid contraceptive and cardiovascular disease area include projects in the prevention of hypertension in OC users, lipoprotein changes in monkeys exposed to various OC preparations, and the relationship between contraceptive steroid plasma levels with levels of biochemical risk factors for cardiovascular disease.

In the steroid contraceptives and neoplasia program area, two contracts were completed and one contract on the occurrence of breast, endometrial, an ovarian cancer proceeded on schedule. Contracts completed include those on OC use and the occurrence of secondary amenorrhea and pituitary adenoma, and OC use and the occurrence of malignant melanoma.

In two case-control studies on the relative risk of malignant melanoma of the skin among women on contraceptive steroids have been completed, findings are not consistent with the possibility that oral contraceptive users, who had taken the pill for a long time, are at an increased risk of developing melanoma of the skin. Previous studies that did not control for amount of sunlight exposure had given varying results. Similarly, a case-control study on pituitary adenoma in oral contraceptive users has also been completed in the Fiscal Year 1982. This study indicates that there is no correlation between the occurrence of pituitary adenomas and previous pill use. It appears, rather, that pituitary adenomas are being diagnosed in increasing numbers of women with secondary amenorrhea. This latter phenomenon may have given rise to the notion that pituitary adenomas may have been a risk of steroid contraceptive use.

The largest ongoing case-control study in neoplasia and the use of steroid contraceptives has been a study designed to evaluate the relationship between oral contraceptive use and the occurrence of breast, endometrial, and ovarian cancer by means of a population-based case control study. Preliminary analyses of data from this study provide no support for earlier reports that oral contraceptive use increases the risk of cancer. Furthermore, the data indicate that oral contraceptive use seems to decrease the risk of endometrial and ovarian cancer. The data collection phase of this project will proceed through December 31, 1982. When data collection is completed, it is anticipated that information will be available for about 4650 cases of breast cancer, 725 cases of endometrial cancer, and 650 cases of ovarian cancer.

In the program on steroid contraceptives and diabetes mellitus, a large case-control study on the risk of diabetes in current and past users of oral contraceptives was completed during the 1982 Fiscal Year. It now seems unlikely that use of contraceptive steroids will be statistically associated with the overall increase in the risk of diabetes mellitus among all users. Further work on more refined populations at risk would seem to be indicated since it is likely that only those women biologically predisposed to insulin exhaustion are likely to develop overt insulin dependent diabetes. Further work on carbohydrate intolerance in populations at high risk of developing diabetes will serve as the future focus of this program.

Intrauterine Devices and the Risk of Infertility

The overall goals of intrauterine device research programs relate to understanding the medical effects and the mechanism of action of intrauterine devices. Ongoing programs exist in the area of evaluation of the effects of intrauterine devices and other contraceptive methods on the occurrence of undesired infertility. Newer programs will be developed to study the mechanisms by which IUDs cause pelvic inflammatory disease as well as to determine the mechanism of action of IUDs in humans.

In Fiscal Year 1982, two contracts proceeded to evaluate the relationship between birth control practices and the occurrence of subsequent, undesired infertility. The motivation behind these specific contracts lies in the fact that there has been substantial concern expressed that the use of intrauterine devices may increase the risk of undesired infertility. In both contracts, cases are women diagnosed with non-congenital, female factor infertility. Using case-controlled study designs, women selected as controls are those who have given birth during the calendar use following the year that the associated case tried to become pregnant. Data analysis will focus on estimating the relative and attributable risk of infertility for users of the intrauterine device. In one of the contracts, further analysis will be undertaken to assess the role of past induced abortions in the occurrence of undesired infertility.

Sterilization

The goal of research programs in sterilization are to study the success and immediate and long-term medical effects of sterilization in men and women and to determine the likelihood of success in reversing these effects. To date, the Contraceptive Evaluation Branch has focused its efforts on identifying the long-term sequelae of vasectomy and on evaluating the role of vasectomy in the progression and regression of atherosclerosis. Programs in female sterilization will be undertaken in the next fiscal year.

A major collaborative cohort study has been underway to identify the range and extent of long-term health hazards that may be associated with vasectomy as a contraceptive procedure. Because of reports of adverse effects in animals, and because of the fact that antibodies to sperm have been detected in men post-vasectomy, this large, ongoing cohort study has been supported by the Contraceptive Evaluation Branch. Results of the study will be released at the end of 1982, in the next fiscal year. When the results are published, the Contraceptive Evaluation Branch will be able to make statements regarding whether there is an increase of immune related disorders, atherosclerosis and myocardial infarction, and other disorders in men who are up to 8-10 years post-vasectomy.

Additional epidemiological studies of vasectomy, specifically designed to quantify the risk of coronary heart disease and myocardial infarction, have also been underway in the Contraceptive Evaluation Branch. Two classical case-control studies, respectively identifying myocardial infarction and coronary heart disease patients as well as appropriate controls, have been proceeding for the last four years. In the coronary heart disease contract, men enrolled in an exercise testing registry who have had either angina pectoris, documented myocardial infarction, or resuscitated cardiac arrest are included. Vasectomy history is obtained by questionnaire from these men. Statistics on the risk of myocardial infarction and coronary heart disease in vasectomized men will be computed some time in early 1983. These two case control studies along with the open ended medical surveillance of vasectomized men in the cohort study, above, should yield definitive evidence regarding the long-term sequela of vasectomy. In the meantime, a study in monkeys has been continuing on the effects of vasectomy on atherogenesis. In this latter study, the role of controlled diet can be factored

into the vasectomy atherosclerosis equation. Whether atherogenesis is reversed by reanastomosis of the vas will also be determined in the animal study. Results will be completed in 1983.

Barrier Methods

The goal of the barrier methods program is to assess both adverse and beneficial effects of the mechanical methods of contraception, including the use of spermicides. Two areas of program activity were underway in the 1982 Fiscal Year. The first of these involves soliciting contracts for the design of three case-control studies whose purposes are to evaluate the finding that spermicide use may be associated with an increase risk of congenital defects in offspring of users. Accordingly, a major case-control study is to be undertaken on the association between hypospadias, limb reduction defects, and congenital neoplasia. Approximately 375 live born cases of these defects will be evaluated for mothers' use of spermicidal creams, foams, jellies, and inserts, during the peri-conception period. A second case-control study seeks to identify the association between Downs Syndrome, identified at amniocentesis and the use of spermicides, ascertained prior to karyotyping results. The last case-control study to be undertaken seeks to identify the association between spontaneous abortions and a similar use of spermicidal chemicals in the peri-conception period.

The other major program area being developed in the barrier methods program seeks to study the putative protective effects of mechanical barrier contraception methods, with and without the use of spermicides, against the occurrence of common venereal diseases and pelvic inflammatory disease. A contract program for microbiological sensitivity testing of commonly used spermicidal preparations will be performed in association with a clinical trial of likely effective commercial preparations. The purpose of the clinical trial will be to identify whether the probability of infection with venereal disease is decreased when barrier methods are employed.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Contract Title : Secondary Amenorrhea, Pituitary Adenoma and Oral Contraceptives

<u>Contract No.</u>	<u>Contractor</u>	<u>Money Allocated</u>			
		No	FY	1982	Funds
N01-HD-7-2834	Johns Hopkins University	"	"	"	"
N01-HD-9-2810	University of Southern California	"	"	"	"
N01-HD-9-2811	Johns Hopkins University	"	"	"	"
N01-HD-9-2812	University of California, San Francisco	"	"	"	"

Objectives: These contracts supported a collaborative case-control study to determine relationships between secondary amenorrhea, pituitary adenoma and previous use of oral contraceptives. Patients meeting specified criteria for secondary amenorrhea and/or galactorrhea, prolactin-secreting pituitary adenoma, or elevated prolactin levels, were interviewed to determine their contraceptive history. Data for comparison were obtained from matched normal controls. The data have been analyzed to determine whether oral contraceptive use was more common or of longer duration in patients with pituitary adenoma or secondary amenorrhea than in the controls.

Major Findings: Data were obtained in 212 case-control pairs in which the cases had surgically or radiologically confirmed prolactin-secreting pituitary adenomas, 119 pairs in which the diagnosis in the cases was considered equivocal (i.e., elevated prolactin levels with normal or equivocal radiological findings), and 138 pairs in which the cases had secondary amenorrhea and/or galactorrhea without evidence of prolactin-secreting tumor. The distribution of duration of use of oral contraceptives for patients in these three groups and their respective controls was very similar. The relative odds of ever having used oral contraceptives were 1.33 for pituitary adenoma cases (95% confidence interval 0.81-2.22), 1.35 for the equivocal cases (95% CI 0.69-2.70), and 0.67 for women with secondary amenorrhea and/or galactorrhea but no evidence of tumor (95% CI 0.37-1.18). These odds are not significantly different from unity and the data indicate no increase in risk of developing prolactin-secreting pituitary adenomas in relation to previous use of oral contraceptives.

Significance to Biomedical Research and the Program of the Institute: Pituitary adenomas are being diagnosed in increasing numbers of women with secondary amenorrhea. This may be the result of improved radiographic and radioimmunoassay techniques which can now identify very small tumors, or it may be that these tumors are increasing in frequency. Many of these tumors have been reported in women who have discontinued use of oral contraceptives. This study indicates that there is no correlation between the occurrence of pituitary adenomas and previous pill use.

Proposed Course: Work under these contracts has been completed.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Intraagency Agreement Title: Oral Contraceptive Use and the Risk of Breast, Endometrial, and Ovarian Cancer
Intraagency Agreement Number: Y01-HD-8-1037
Agency: Centers for Disease Control, Atlanta, Georgia
Money Allocated: \$1,088,025

Objectives: To evaluate the relationship between oral contraceptive use and the occurrence of breast, endometrial and ovarian cancer by means of a population-based, case-control study.

Major Findings: In this study, women with the three forms of cancer being investigated are compared to healthy women to determine whether there are differences in histories of oral contraceptive use. The cancer cases are identified from the Surveillance, Epidemiology, and End Results network of cancer registries that the National Cancer Institute has established across the United States. The controls are identified by a random digit dialing procedure from the same populations as the cases. The study began May 1, 1978. During the developmental phase, the study design, data instruments, and operational procedures were refined and field-tested. Contracts for case-ascertainment and interviewing were established with the SEER centers, and a contract for random digit dialing was established with Westat Corporation. The data collection phase began December 1, 1980. During the first six months of data collection, information was obtained concerning 689 cases of breast cancer, 187 cases of endometrial cancer, 179 cases of ovarian cancer, and over 1800 controls. Preliminary analyses of these data provide no support for earlier reports that oral contraceptive use increases the risk of breast cancer. Furthermore, the data indicate that oral contraceptive use decreases the risk of endometrial and ovarian cancer.

Significance to Biomedical Research and the Program of the Institute: The relationship between oral contraceptive use and the occurrence of breast, endometrial, and ovarian cancer is an issue of major public health importance. This study is designed to provide detailed information concerning this issue.

Proposed Course: The data collection phase will proceed through December 31, 1982. When data collection is complete, it is anticipated that information will be available for about 4,650 cases of breast cancer, 725 of endometrial cancer, 650 of ovarian cancer, and 4,725 controls. Detailed analyses will then be carried out. These will examine the effect of oral contraceptive use on the occurrence of all three cancers, with specific attention to possible interactions between oral contraceptive use and other factors that influence the occurrence of these cancers (such as family history). Numerous publications are anticipated.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Contract Title: Case-Control Study of the Relative Risk of Malignant
Melanoma of the Skin Among Women on Contraceptive Steroids
Contract Number: N01-HD-8-2803
Contractor: University of California, Los Angeles, California
Money Allocated: \$350,234

Objectives: These were to estimate the relative risk of malignant melanoma in women exposed to steroid contraceptives taking confounding variables of sunlight exposure and sun sensitivity into account. One hundred fifty incident cases were to be ascertained from the two population-based tumor registries in Los Angeles and the five county San Francisco Bay area. Incidence cases were preferred to prevalence cases since the effect of steroid contraceptives on survival time is not known and to avoid errors in recall and other biases in the interpretation and generalizability of results. For each case, two controls were to be selected, one of which was to be a longstanding friend, the second a neighbor. Both were to be matched for age and skin color. They serve as partial controls for life-style, sun exposure and sun sensitivity, judged from complexion and skin color. Variables not matched in the design were to be analyzed as covariates. Both matched pair and covariate analysis were used.

Major Findings: Both the operational phase of the project in Los Angeles and the San Francisco Bay Area, and the analytical phase performed in Los Angeles have been completed. As yet, the Final Progress Report has not been received by NICHD. However, the Project Officer of NICHD was informed about its content and assured it would be mailed in the immediate future.

The following contents of the Final Progress Report were summarized by telephone conversations. Ever-use of oral contraceptives was not associated with an increased risk of melanoma. Contrary to the suggestion from Contract-HD-8-2804, there was no trend of increasing relative risk with increasing total time of pill use. An increased risk was not observed among women with a total time of pill use of five years or longer who first began using it ten or more years ago. These findings are not consistent with the possibility that a small fraction of oral contraceptive users who had taken the pill for a long time and began using it many years ago are at an increased risk of melanoma. The principal investigator of this contract explains all contrary conclusions by other investigators as due to the failure to correct for confounding factors, e.g., increased sunlight exposure of oral contraceptive users.

Significance to Biomedical Research and Program of the Institute: This work and its conclusion add to the growing evidence that oral contraceptives do not cause malignant disease. It confirms the most important conclusions from Contract-HD-8-2804 and explains the less convincing conclusions from this latter project as due to the failure to rigorously analyze for confounding factors.

Proposed Course: The project is completed except for receipt of the final report. A workshop to evaluate the project's conclusions is being considered.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Contract Title: Case-Control Study of the Relative Risk of Malignant
Melanoma of the Skin Among Women on Contraceptive Steroids
Contract Number: N01-HD-8-2804
Contractor: University of Sydney, Sydney, Australia
Money Allocated: \$109,317

Objectives: These were to characterize the association between the use of oral contraceptives and occurrence of malignant melanoma, the determination of relative risk, causative and confounding factors. The most recent 300 prevalent cases in women aged 15-49 years, diagnosed since 1970 were to be ascertained from the files of the Sydney Hospital, Melanoma Unit. Further, 100 incident cases were to be ascertained as they were diagnosed in Sydney Hospital during the first 18 months of this contract. For each case selected, one neighborhood and one hospital control matched by years of birth was to be ascertained. Cases and controls were to be interviewed using a questionnaire to obtain contraceptive reproductive history and sunlight exposure. The presence of confounding factors was to be sought by stratification of data according to age, parity, marital status, sunlight exposure, skin color or sun sensitivity. It was projected to be able to detect a relative risk of 1.8 with 90% certainty at a 1% significance level.

Major Findings: The operational phase of the project carried out in Australia and the analytical phase performed in London, England have been completed. The final progress report has been received by NICHD. The following results were obtained.

Ever use of oral contraceptives was not associated with an increased risk of melanoma (relative risk= 1.01, 95% confidence limits 0.81 to 1.81). On the other hand, there seemed a trend of increasing relative risk with increasing total time of pill use. Increased risk was confined to those with a total time of pill use of five years or longer who first began using the pill at least ten years ago (relative risk = 1.48, $p < 0.05$, 95% confidence limits 1.10 to 1.62). The findings suggest the possibility that a small fraction of oral contraceptive users who had taken the pill for a long time and began it many years ago are at a slightly increased risk of melanoma. However, very few women have taken the pill for so long; only 15 percent of controls in Dr. Beral's study had taken the pill for a total of five years or more and began using it more than 10 years ago. These figures would probably be lower in countries where oral contraceptive use is less prevalent than in Australia. The maximal increase in risk in Australia was small too and oral contraceptive use could make little contribution to the overall etiology of melanoma. Search for confounding factors, e.g., sunlight exposure was unrewarding in that the slight increase in relative risk associated with long duration of pill use persisted.

Significance to Biomedical Research and Program of the Institute: The work and its conclusion add to the growing evidence that oral contraceptives do not cause malignant disease. Dr. Beral's conclusion that ever use of oral contraceptives is not associated with an increased risk of melanoma is more convincing than all published contradictory conclusions.

Proposed Course: The project is completed. A workshop to evaluate and/or adopt the project's conclusions is being considered.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Contract Title : Research on the Presence of Abnormal Proteins in the Serum
of Oral Contraceptive Users
Contract No. : N01-HD-0-2823
Contractor : Emory University
Money Allocated: \$99,202

Objectives: The purpose of this project is to confirm and extend work of Beaumont et al. on an abnormally precipitating globulin (GAP) found in the serum of some women using oral contraceptives. Beaumont reported that this protein fraction was elevated in a significant number of healthy users and ex-users of oral contraceptives and markedly elevated in most women with serious thrombotic complications of pill use. Under this contract, efforts are being made to reproduce the laboratory procedures used by Beaumont and to measure levels of GAP in serum of current OC users, ex-users, never-users, new users studied longitudinally, and patients with thrombotic episodes associated and not associated with pill use. The possible occurrence of racial differences between black and white women is being explored in samples of never- and current users.

Major Findings: The investigators supported by this contract and by N01-HD-0-2824 have worked collaboratively in efforts to determine precisely the laboratory procedure used by Beaumont in Paris. After extensive communications, comparable procedures now appear to be established in the two contract laboratories. The target population for the Emory University contract includes 100 never-users, 50 current users, 50 new users to be studied longitudinally, 50 ex-users, and 20-50 patients with thrombosis. This population is expected to be reached by the end of the current fiscal year. Preliminary analyses of partial data do not confirm Beaumont's findings.

Significance to Biomedical Research and the Program of the Institute: If Dr. Beaumont's findings can be confirmed, this would help to elucidate the mechanisms involved in the development of thrombotic disease in users of oral contraceptives. It could also provide a method for identifying women at special risk of OC-induced thrombosis, and these women could be advised to use other means of contraception.

Proposed Course: It is anticipated that work under this contract will be completed this year.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Contract Title : Research on the Presence of Abnormal Proteins in the Serum
of Oral Contraceptive Users
Contract No. : N01-HD-0-2824
Contractor : Wayne State University
Money Allocated: \$43,179

Objectives: The purpose of this project is to confirm and extend work of Beaumont et al. on an abnormally precipitating globulin (GAP) found in the serum of some women using oral contraceptives. Beaumont reported that this protein fraction was elevated in a significant number of healthy users and ex-users of oral contraceptives and markedly elevated in most women with serious thrombotic complications of pill use. Under this contract, efforts are being made to reproduce the laboratory procedures used by Beaumont and to measure levels of GAP in serum of current OC users, ex-users, never-users, and patients with thrombotic episodes associated and not associated with pill use. The user group includes women taking oral contraceptive preparations with high and low estrogen content.

Major Findings: The investigators supported by this contract and by N01-HD-0-2823 have worked collaboratively in efforts to determine precisely the laboratory procedures used by Beaumont in Paris. After extensive communications, comparable procedures now appear to be established in the two contract laboratories. The target population for the Wayne State contract includes 100 never-users, 50 users of combination oral contraceptives with low estrogen, 50 users with high estrogen, 50 ex-users, and 20-50 patients with thrombosis. This population is expected to be reached by the end of the current fiscal year. Preliminary analyses of partial data do not confirm Beaumont's findings.

Significance to Biomedical Research and the Program of the Institute: If Dr. Beaumont's findings can be confirmed, this would help to elucidate the mechanisms involved in the development of thrombotic disease in users of oral contraceptives. It could also provide a method for identifying women at special risk of OC-induced thrombosis, and these women could be advised to use other means of of contraception.

Proposed Course: It is anticipated that work under this contract will be completed this year.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Contract Title : Longitudinal Studies of Lipoprotein Changes in Users of Various Oral Contraceptive Preparations
Contract No. : N01-HD-1-2803
Contractor : George Washington University
Money Allocated: \$375,868

Objectives: To evaluate the effects of three currently marketed oral contraceptive formulations on lipoprotein patterns, glucose tolerance, and insulin secretion in women.

Major Findings: This project, which began June 1, 1981, is a prospective clinical investigation of the effects of three currently marketed oral contraceptive (OC) formulations on lipoprotein patterns, glucose tolerance, and insulin secretion in women. The study design specifies that 300 women 18-30 years of age who wish to initiate OC use be randomly assigned to one of three OC formulations, each containing 50 mcg of ethinyl estradiol and either 1 mg of ethynodiol diacetate, 1 mg of norethindrone acetate, or 0.5 mg of norgestrel. A control group of 100 women not using OCs will also be studied. At specified intervals prior to, during, and after OC use, blood specimens will be obtained and analyzed for fasting glucose, glucose tolerance, insulin levels, hemoglobin A_{1c}, and a variety of lipid components (including high-density lipoprotein cholesterol and "beta quantification"). Medical histories will be reviewed and physical examinations will be performed. Twenty-four hour dietary recalls and exercise histories will be recorded. The data from the project will be analyzed to determine the effects of the three OC formulations studied on lipoprotein pattern and glucose tolerance. Confounding or interaction with factors such as diet and exercise will be examined.

The data collection phase began in the fall, 1981. For several months, subject recruitment proceeded very slowly. In early 1982, the problems that were hindering recruitment were evaluated, and a new strategy was developed that emphasized "media" advertising. Thus far, this strategy has been very successful. For example, an article describing the study that appeared in the Washington Post newspaper resulted in 175 inquiries from women interested in the study. Of these, 19 have been found eligible and have been enrolled. It is anticipated that further recruitment efforts of this type will yield a sufficient number of eligible subjects for the study to proceed.

Significance to Biomedical Research and the Program of the Institute: It is currently believed that some OC formulations may increase the risk of cardiovascular disease by accelerating the process of atherogenesis, and may do this by altering lipoprotein patterns (e.g., by decreasing high-density lipoprotein cholesterol), and glucose tolerance. This study will provide detailed information concerning the effects of 3 widely used OC formulations on lipoprotein patterns and glucose tolerance.

Proposed Course: Subject recruitment is currently scheduled for completion by the end of 1982. Although some extension of recruitment may be necessary, recent efforts have been very encouraging (see above). When recruitment is complete, data collection will continue until each subject has been studied for one year. when data collection is complete, data analysis and interpretation will be carried out. Publication of findings will ensue.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Contract Title: Health Status of American Men

<u>Contract Number</u>	<u>Contractor</u>	<u>Money Allocated</u>
NO1-HD-6-2807	University of California at Los Angeles	\$353,900
NO1-HD-7-2801	Mayo Clinic	39,430
NO1-HD-7-2802	University of Southern California	266,180
NO1-HD-7-2803	University of Minnesota	225,000

Objectives: The purpose of this collaborative study is to identify long-term health hazards which may be associated with vasectomy as a contraceptive procedure. The current health status and medical histories of previously vasectomized men are to be compared with those of non-vasectomized control groups. The contracts with the Mayo Clinic, USC and the University of Minnesota provide for data collection according to a common protocol, and the contract with UCLA provides for project coordination and data analysis.

Major Findings: In the first phase of this study, a detailed protocol and manual of procedures was developed and subjects for the study were identified. Data collection is now nearing completion and information has been obtained and processed on over 9,905 matched case-control pairs of subjects. Plans for analysis are well under way but analyses of possible differences between cases and controls have been deferred pending completion of data collection in order to avoid any possibility of introducing bias into the collection of the remaining data.

Significance to Biomedical Research and the Program of the Institute: Vasectomy is a popular method of contraception which has generally been considered to have no serious adverse effects. However, it is known that a substantial proportion of vasectomized individuals develop circulating antibodies to spermatozoa and that, in rabbits, guinea pigs, and monkeys, this immune response can result in disease in the testis and sometimes kidney. Furthermore, in monkeys there is now evidence that vasectomy leads to exacerbation of atherosclerosis, presumably through immunologic injury to arterial walls. This study will be able to identify differences in incidence of common and also quite rare diseases in vasectomized men as compared to controls, or to demonstrate that there is no increase in risk within certain defined limits of probability, for intervals up to 8-10 years after vasectomy.

Proposed Course: Data collection has been completed at the Mayo Clinic and will be completed in Los Angeles and Minneapolis this year. The remainder of calendar year 1982 will be required for analyses of the data and preparation of a summary report and a monograph describing the study and reporting its findings.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Contract Title : Effect of Bilateral Vasectomy on the Progression and Regression of Atherosclerosis in Macaca fascicularis
Contract No. : NO1-HD-8-2827
Contractor : Oregon Regional Primate Research Center and Bowman Gray School of Medicine
Money Allocated: \$67,500

Objectives: The purpose of this contract is to pursue preliminary findings which indicated that vasectomy may significantly increase the severity of atherosclerosis in monkeys. The effects of vasectomy on atherogenesis are being studied in normocholesterolemic and hypercholesterolemic monkeys fed a diet comparable in cholesterol content to that of the average North American man. The possible therapeutic role(s) of a more prudent diet and/or vas reanastomosis on regression of established atherosclerosis will also be evaluated.

Major Findings: Sixty cynomolgus monkeys which had been under study at Bowman Gray have been necropsied and the extent of atherosclerosis in the thoracic and abdominal aortas and coronary arteries has been evaluated. The original finding of exacerbation of atherosclerosis has been confirmed but the effect is not seen in all animals--about one third of the monkeys showed no effect, one third some increase, and one third a marked increase in the extent and severity of atherosclerosis. The most extensive plaque formation was seen in those vasectomized monkeys which, while maintained on the standard diet, developed the highest blood cholesterol levels and the highest cholesterol/HDL cholesterol ratios. The data for the coronary arteries are similar although the effect is less pronounced. Efforts to identify deposits of immune complexes in specimens from arteries, kidney, liver and spleen by immunofluorescent techniques have given negative results.

Fifteen of the 75 monkeys at Oregon have been sacrificed for similar evaluations and 23 have been excluded from the study because efforts to reanastomose the vas deferens were unsuccessful. The remaining 37 include 20 with successful vasovasostomy and 17 in which there has been no surgical intervention since vasectomy. In view of the reduced numbers of monkeys, studies of the effects of restriction of dietary lipids have been dropped.

Significance to Biomedical Research and the Program of the Institute: These contractors have previously shown in pilot studies that vasectomy markedly increased the extent of atherosclerosis in two species of monkeys. This contract was designed to validate and extend these preliminary data and to determine the possible therapeutic role of vas reanastomosis and/or restriction of dietary lipids in regression of established atherosclerosis. As noted above, it will not be possible to evaluate the role of reduced dietary lipids in the regression studies.

Proposed Course: The extent of atherosclerosis will be quantitated in the remaining arteries from the 60 monkeys sacrificed at Bowman Gray. The 37 monkeys remaining in the regression studies will be maintained until January 1983 and then sacrificed for similar assessment of the levels of atherosclerosis in the major arteries.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Contract Title : Epidemiologic/Clinical Studies of Vasectomy and Atherosclerosis
Contract No. : N01-HD-0-2806
Contractor : Medical College of Wisconsin
Money Allocated: No FY 1982 Funds

Objectives: The purpose of this study was to determine whether there is a relationship between vasectomy and the extent of coronary artery atherosclerosis in man. The cardiovascular status of the 11,000 members of the Milwaukee Cardiovascular Data Registry had previously been evaluated by coronary angiography. The contract provided for collecting data on vasectomy history, combining this with the angiographic data and available data on established cardiovascular risk factors, and analyzing the results to determine relationships between vasectomy and the extent of coronary artery occlusion.

Major Findings: The results of this study demonstrate no association between vasectomy and the degree of coronary artery occlusion. Among the 7,420 men who responded, 5.0 % reported having had a vasectomy prior to angiography. There was no excess frequency of vasectomized men, or men vasectomized for long intervals, among men with higher occlusion scores. Overall, 7.1% of the men with low occlusion scores had been vasectomized while only 3.9% of the men with high occlusion scores had been vasectomized. In addition to overall comparisons, matched pairs analyses were used comparing each vasectomized man with four age-matched controls, and multiple regression techniques were used to assess the role of risk factors thought to be associated with the degree of coronary occlusion. Analyses were also conducted on subgroups of the patients with extensive and minimal coronary artery occlusion. The results showed that the vasectomized men did not have a higher degree of coronary occlusion than their age-matched controls. In fact, the only trend noted was in the opposite direction, the vasectomized men having a significantly lower degree of coronary occlusion than the controls. There did appear to be a weak association between vasectomy and a history of hypertension when univariate analytic techniques were used but this was not demonstrable when multivariate techniques were employed.

Significance to Biomedical Research and the Program of the Institute: Data from two NICHD contract studies have now demonstrated that vasectomy results in marked exacerbation of atherosclerosis in two species of monkeys. The possibility has thus been raised that vasectomy, a popular method of permanent contraception, may lead to a significant increase in risk of human cardiovascular disease. This contract provides the first information from a case-control study specifically directed to the question of a possible association between atherosclerotic disease and vasectomy in man.

Proposed Course: Work on this project has now been completed.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Contract Title : Epidemiological Study of Vasectomy and Coronary Heart Disease
Contract No. : N01-HD-0-2809
Contractor : Battelle Memorial Institute
Money Allocated: No FY1982 Funds

Objectives: The purpose of this project is to determine the relationship between vasectomy and the subsequent development of coronary heart disease. The study involves men enrolled in the University of Washington Exercise Testing Registry who have had angina pectoris, myocardial infarction or resuscitated cardiac arrest, and control subjects who have no indication of coronary heart disease. Vasectomy history is obtained by questionnaire. Data on the prevalence of vasectomy and duration of exposure will be compared in the two groups. Data will also be analyzed to take into consideration other known and suspected risk factors for cardiovascular disease.

Major Findings: Recruitment of all study subjects has been completed and data have been obtained on over 6,000 men. Analyses are now in progress. The rate of vasectomy in this population is over 30%, as is typical for white, middle-class men living on the West Coast. Since 60% of the vasectomized men had the surgery 10 years or more before follow-up, and nearly 30% 20 years previous to follow-up, the data should permit an assessment of the risks associated with long exposure to the effects of vasectomy.

Significance to Biomedical Research and the Program of the Institute: Data from two NICHD contract studies have now demonstrated that vasectomy results in marked exacerbation of atherosclerosis in two species of monkeys. The possibility has thus been raised that vasectomy, a widely used method of permanent contraception, may lead to a significant increase in risk of human atherosclerotic disease. This contract is expected to provide important information on the role of vasectomy as a possible risk factor for coronary heart disease in man.

Proposed Course: Data analyses will be completed at the end of 1982.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Contract Title : Study of Myocardial Infarction in Relation to Vasectomy
Contract No. : N01-HD-0-2810
Contractor : Boston University Drug Epidemiology Unit
Money Allocated : \$374,600

Objectives: The purpose of this contract is to determine the relative risk of myocardial infarction in vasectomized as compared to non-vasectomized men. A classical case-control study is being conducted in some 75 hospitals in New England and New York State. Cases are male patients under age 55 admitted for first myocardial infarction and controls are men admitted to the same hospitals for unrelated acute conditions. Interviews are used to obtain information on vasectomy history and other known or suspected risk factors for cardiovascular disease. It is anticipated that some 2000 cases and 1-2 controls per case will be enlisted over a three year period of data collection.

Major Findings: Data collection is progressing well and more than half the anticipated cases have now been interviewed. No findings can be expected at this time, but it is noteworthy that over 4% of the control subjects report having been vasectomized 10 or more years before hospitalization. The study therefore will be able to detect a relative risk of 1.5 for myocardial infarction at 10 years after surgery if such a risk exists.

Significance to Biomedical Research and the Program of the Institute: Data from two NICHD contract studies have now demonstrated that vasectomy results in marked exacerbation of atherosclerosis in two species of monkeys. The possibility has thus been raised that vasectomy, a widely used method of permanent contraception, may lead to a significant increase in risk of human atherosclerotic disease. This contract is expected to provide important information on the role of vasectomy as a possible risk factor for myocardial infarction in man.

Proposed Course: Another year will be required to complete the data collection and analysis.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Contract Title : Birth Control and the Risk of Infertility
Contract No. : N01-HD-0-2821
Contractor : University of Washington
Money Allocated: 0

Objectives: To evaluate the relationship between birth control practices and the occurrence of subsequent, undesired infertility by means of a population-based case-control study.

Major Findings: In this study, cases are all women 20-39 years of age with non-congenital, female-factor infertility that are identified from medical evaluations for apparent infertility in King County, Washington during a three-year period. For each case, one matched (for age, census tract, marital status, and pregnancy order) control is being studied. This is a woman who gave birth during the calendar year following the year that the associated case began trying to become pregnant. Cases and controls are being interviewed to obtain demographic, personal, medical, and reproductive history, with a detailed history of birth control practices. Data analysis will focus on estimating the relative and attributable risk of infertility for users of the intrauterine device, for women who have undergone induced abortions, etc. as compared to women who have not used these methods of birth control.

This project began June 30, 1980. The first six months was devoted to preparatory work. The study protocol was refined, an interviewer's manual was prepared, and forms were developed for recording interviews and for abstracting medical records. Approval for investigating human subjects was obtained, and procedures for identifying and contacting potential cases and controls were established.

Data collection began January 1, 1981. By March 19, 1982, interviews had been completed for 576 cases and 136 controls. An additional 474 cases and 404 controls had been identified and were in the process of being contacted for interview. Medical records had been abstracted for 40 cases. All completed interviews had been coded and edited for entry on to computer files. Data entry had been completed for 130 cases and 136 controls. All data management and analysis systems were operational.

Significance to Biomedical Research and the Program of the Institute: Substantial concern has been expressed over the possibility that the use of intrauterine devices may increase the risk of subsequent infertility. This project is designed to investigate this issue, and provide an estimate of the risk of infertility that is attributable to the use of intrauterine devices or other methods of birth control.

Proposed Course: The data collection phase of the project is scheduled for completion by December 31, 1982. When data collection is complete, it is anticipated that information will be available concerning approximately 1500 female-factor infertility cases and 1500 controls. Data analysis will begin in the fall of 1982; data analysis and report preparation will continue for approximately six months after data collection is complete.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Contraceptive Evaluation Branch
Contract and Collaborative Research

Contract Title : The Relationship Between Birth Control Practices and
Occurrence of Subsequent Undesired Infertility
Contract No. : N01-HD-0-2822
Contractor : Boston Hospital for Women
Money Allocated: 0

Objectives: To evaluate the relationship between birth control practices and the occurrence of subsequent, undesired infertility by means of a clinically-based, case-control study.

Major Findings: In this study, cases are married women over 18 years of age who are identified as having female factor infertility at seven clinical centers across the United States. Controls are: (1) women from infertile couples whose infertility is due to male factors, and (2) recently delivered women. Cases and controls are interviewed to obtain information concerning birth control practices and other relevant data. Analysis will focus on estimating the relative risk of female factor infertility in women who have used IUDs, undergone induced abortions, etc. as compared to women who have not used these methods of birth control.

The study began June 30, 1980. During the first nine months, the study protocol was refined, data forms were developed, and subcontracts with the clinical and statistical collaborators were established. Data collection began April 1, 1981. As of April 30, 1982, 1,001 female factor infertility cases and male factor infertility controls, and 1,379 recently delivered controls, had been interviewed. 2,117 of the interview forms had been entered on to the computer file. 1500 of these interviews had been examined for internal consistency via a logical error program.

Significance to Biomedical Research and the Program of the Institute: Substantial concern has been expressed that the use of intrauterine devices may increase the risk of subsequent infertility. This project will provide detailed information concerning this issue

Proposed Course: Data collection for this project is scheduled for completion by March 30, 1983. When data collection is complete, it is anticipated that information will be available concerning approximately 1000 cases of female-factor infertility, 1000 male-factor infertility controls, and 2400 recently delivered controls. Although some problems have been encountered in completing the computer programs for data processing and analysis, these problems are being overcome. It is anticipated that an "analytic file," which will contain information on cases and controls that have been fully investigated, will be operational by May. Preliminary analysis of data will begin in the summer or fall 1982. As the study approaches completion of data collection in early 1983, efforts will be gradually shifted towards data analysis. Data analysis and report preparation is scheduled for completion approximately six months after completion of data collection.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Grant, Contract and Collaborative Research

The grant and contract program of the Social and Behavioral Sciences Branch (SBSB), Center for Population Research, focuses on the size, rate of growth, and composition of our nation's most important asset, its population. The topics addressed by specific research projects derive from fundamental questions concerning the growth and distribution of our population, and their relation to individual and societal welfare. For example: What accounts for changes in the number of children couples decide to have? What affects their degree of success in controlling their reproduction? How do families and households form and reform? What are the consequences of many or few children for individuals, families, and the nation? What are the effects of age at childbirth and birth spacing on mothers, fathers and their children? How does internal migration affect the welfare of the people moving and the communities from which they come and to which they go? How would a rise or decline in the rate of population growth from a combination of natural increase and net immigration affect our economy and our environment in the future? Answers to these and many other questions are needed in order to deal with population changes now and in the years ahead. The results of research are intended ultimately to help individuals and couples understand the personal and societal consequences of their behavior and to help the government evaluate the impact of a variety of policies and programs on both the quantity and quality of our human resources.

The staff of the SBSB uses grants to support research on these broad objectives, and uses contracts to support research on more specific research goals identified as critical to the mission of the Institute.

The Branch's strategy has been to concentrate on topics of current societal importance as well as questions of basic scientific concern. Consequently, the program has emphasized not only such topics as social and economic factors affecting the level and trend in national birth rates, but also the effectiveness of contraceptive practice, changes in family size and their consequences, the determinants and consequences of adolescent fertility, trends and implications of delayed childbearing, the economic, social, and psychological costs and benefits of children, the implications of immigration for the U.S., and an analysis of changing family and household structure. The Branch has a continuing interest in promoting research to improve methodology for population research, and providing synthesized research resources of value to the scientific community. The Branch's research program changes in response to changing social conditions as well as in response to developing scientific knowledge. At present, its program focuses on the topics listed below.

Family and Household Structure

The family has been the institution that traditionally created the context for childbearing, the development and maintenance of individuals and support of the elderly. Households define the living arrangements of families, and the concept of household and family in the U.S. have been virtually synonymous. In recent years, the structure of the American family has changed. The manner in which the family functions in its traditional role of producing, developing, and maintaining its component individuals has undergone changes parallel to that of its structure.

Testimony to these events is given by the recent explosion in the number and type of households that are becoming increasingly divergent from traditional structures. Accordingly, much attention has been given to documenting the components of change contributing to the changing structures characterizing the family and household and the extent of change occurring.

The major focus of the Center's research program to date has been directed toward the measurement of the demographic dynamics contributing to the change in family and household structure. A number of interesting insights have emerged from these studies. First, contrary to popular thought, marriage as an institution seems to be attaining great popularity. For instance, the percent of the population which will experience marriage at least once during their lifetime is rising and the rate of remarriage for those who have experienced divorce is also rising. However, young adults seem to be postponing the time of marriage. Furthermore, divorce rates are rising rapidly, they are not rising as fast as popularly thought. In households undergoing various family transitions, a growing number of children will be exposed to nontraditional family living for a greater proportion of their childhood than in the recent past. When one views these changes from the standpoint of children, a number of issues concerning the development and well-being of children arise which have not been the subject of much research in the past. For example, important questions concerning the effect of marital disruption and nontraditional family living on the development of children are surfacing in the scientific community and the studies funded to date in the CPR research program will be central to answering these questions by enabling us to measure and calibrate the exposure of children to these events.

While marriage has become a virtually universal experience in the American population, one study reports that for white women born since 1940, there has been a distinct upward trend in the median age at marriage. For example, the median age of first marriage for white women born in 1940-44 was about 20.5 years, while for women born 1955-59 it was about 21.9 years. If these trends continue, the median age of first marriage for white women born in 1975-79 may be as high as 24.2 years. For Black women the median age of marriage is much higher and rising more rapidly. Thus, the overall age distribution of first marriage probabilities seems to be returning to those exhibited by a much earlier era and that the white and Black populations seem to be diverging in their recent experience with marriage. Also, the business cycle tends to affect the age at first marriage by causing white women to delay marriage during economic downturns. The marriage patterns of Black women do not appear to respond to business cycles, however.

There has also been a pronounced and rising trend in the fraction of marriages likely to end in divorce. However, recent studies have indicated that refined measurement of the probability of divorce leads to the conclusion that divorce is less common than the popularly quoted statistic that "half of all marriages end in divorce." Based on data from the early 1970s, the fraction of marriages that will end in divorce is 30 percent for women and 25 percent for men. For women, marriages have an even higher probability of ending with their spouse's death (47 percent in the early 1970s). However, for men the risk of a marriage terminating in widowhood (about 18 percent) is below the fraction of their marriages likely to end in divorce.

One interesting indication that marriage is a strong and growing influence in American family life is the rate of remarriage after divorce. While there has been a slight tendency to delay remarrying in recent divorce cohorts, most

divorced persons remarry. Nineteen seventy-five data show that remarriage rates are 74 percent for women and 83 percent for men. Moreover, recent analysis of 1980 data suggests that Americans still consider marriage to be a central aspect of family life.

The confluence of the trends in marriage, divorce, and remarriage are producing a number of families that are combinations of previously existing families. For example, about a third of the children in recent remarriages were under the age five, few were without siblings at the time of remarriage and most of their stepfathers had been married before. Preliminary analysis of recent data suggests a doubling in the children's experience of a second marital disruption. Overall, about one-sixth of all children have step or half siblings, and about a quarter are not living with both of their natural parents; for children of remarried mothers, these proportions are three-fifths with partial siblings and two-thirds not with both natural parents. Another way of looking at the impact of marital disruption on children is to examine the proportion of children who will experience some form of family disruption during their childhood. One study reports that given current trends, more than 40 percent of all children born in 1975-1979, about one-third of white children and seven out of 10 Black children are expected to live with only one parent at some time before reaching the age of 18. Moreover, the time trend in these figures is quite large and this implies that the exposure of children to some form of family disruption will be larger for more recent birth cohorts. These studies set the stage for asking questions of great importance to society in general and population research in particular. Are we entering into a new era in which new social institutions and behavioral patterns will emerge regarding family life, reproduction and child rearing? Are we merely returning to patterns established in an earlier era but interrupted by the dramatic events of worldwide depression and war? Or perhaps will we learn to adapt old institutions and behavior to adjust to markedly different modern conditions?

Another study has examined what happens to contraceptive practice when a marriage ends. The most outstanding finding of this study is that little change in contraceptive regime occurs. Most women report continuation of whatever method they were using previous to the marital disruption, about one in six report that they were not having intercourse during the months in question. This implies that a substantial fraction of women remain sexually active during the period immediately following a marital disruption. This implies that the experience of births between marriages for remarried women (25 percent in 1970) is not so much the consequence of difficulties in obtaining and using contraceptives as it is in a continuation of pre-separation patterns that results in accidental pregnancies that would have otherwise occurred within marriage. This but is one example of how important it is to maintain an awareness of contraception regardless of marital state.

The family and institutions associated with the family, like marriage, are still important and popular aspects of American life. However, the way individuals relate to one another within a family context and ultimately the function of the family with respect to its component individuals may be undergoing considerable transformation. One study suggests that there is a pervasive decrease in the role of kinship in modern societies and that attendant trends in marriage, divorce, fertility, and employment patterns have been strongly affected by the emergence of women in the labor force and an attendant growth in their earning power. A companion study goes on to suggest that these changes have been further accelerated by the development of modern, economic markets and rapid technological change which have increased the productivity of investment in human beings and in

physical capital and which relies increasingly on public institutions to capture a return on these investments rather than in private institutions like the family. Another study suggests that even though families tend to be composed of households which maintain separate residential facilities, the households are clustered physically in such a way that they can still act as a support system within a family context. This is much more the case for elderly persons than for the young. The study also suggests that currently elderly cohorts have access as often (but not more) to family support nearby as do those with family in the household. One study suggests that residential and financial independence of the young are not always sensitive to the same factors. For example, financial dependence of the young on their parents seems to be prolonged by continued education while residential independence is shortened by it.

The proportions of the population living in specific household/family types seem to exhibit sharply contrasting patterns among ethnic groups. One study has compared Mexican-American, Puerto Rican, Cuban, Black, and Anglo populations in the United States with respect to family/household patterns. It is found that the probability of Mexican-American females living alone is quite low, while the prevalence of large multi-adult households is comparatively high for both Mexican Americans and Puerto Ricans. However, Puerto Ricans differ markedly from all other Hispanic populations because of high ratios of women with children who have either never married or whose marriage has been disrupted. The Cuban population has shown a tendency to develop its household structure in the direction of the traditional marriage and family. In comparison, Black households show higher probability of marital disruption and, like Puerto Ricans, a higher probability of households containing single females with two or more children. Each of the race/ethnic populations, except Cubans, tended to follow general societal trends in household/family arrangements between 1960 and 1970. This study illustrates the significant differences among the subpopulations of the Hispanic ethnic group. Indeed it calls into question the value of using a general category like "Hispanic populations" in analyzing family/household trends.

One of several research projects, viewing historical change in the structure of households, has focused on the disappearance of unmarried females in the household. From the turn of the century up through the 1930s nearly every household included one or more females over the age of 30 who were not married and not gainfully employed. Between 1900 and 1970 there was a reduction of nearly 50 percent in the incidence of unmarried females in households and an even greater reduction in unmarried females not in the labor force. The unmarried females who were not in the labor force were a real family resource, called on in times of illness, at childbirth, and other times of crisis. Most of them lived with and took care of household members in exchange for room and board and an opportunity to share in the family estate. This was a mutually beneficial relationship. In modern times this household resource has nearly disappeared. Two other studies have attempted to model the existence of kin as a support network and to predict what the future may hold. One study finds that, compared with earlier periods in which mean family size was larger and there was also much greater dispersion in family sizes, present (and future) numbers of kin are rather low. They indicate, particularly when migration is taken into account, the scarcity of kin in a stationary population as a source of social or financial support. They also indicate the scarcity of kin to assist in the socialization of children and youth. Another study has found that Black women are more likely, relative to whites, to live with either their children or with others than to live alone. Home ownership reduced the probability of living with children rather than living alone among

formerly married women. However, home ownership did not affect the probability of living with either parents or others, relative to the probability of living alone.

Factors Affecting Fertility and Fertility Regulation

Increasing understanding of the factors underlying changes in the fertility of individuals and society is necessary to improving the lives of individuals and the relationships among nations. Investigators are continuing to extend and refine theory and knowledge about the interactions of biological, psychological, social, economic, and other factors affecting fertility and its regulation in the United States and many other countries, from both contemporary and historical perspectives. The World Fertility Survey has provided, and will continue to furnish, comparative data on fertility in many countries.

Several investigators have been giving more than usual attention to societal-level or contextual effects on fertility. The implications of such studies for the development of population programs and policies are considerable. These studies point to another dimension of the determinants of fertility, but do not necessarily lessen the importance of factors which are more individual. They do indicate the need to analyze and understand the interaction of the various antecedents of fertility.

In one study, it was found that contextual effects are as important as individual characteristics in predicting fertility. The investigator tentatively concluded that such effects occur when general social and economic development has been moving towards a more highly integrated society capable of more uniform responses to change. While differentials in fertility based on socioeconomic status and geographic location remain, these are likely to be of lesser importance than changes occurring, and policies being formulated, at the national level.

Societal-level effects are also found where marital fertility declines almost simultaneously in all areas of a country, regardless of socioeconomic characteristics of each area. These findings confirm earlier studies which indicate that family planning and family limitation may at times be diffused very rapidly throughout a country. In another study, it was shown that the negative relationship between education and fertility holds for Mexican-American women, and this relationship was confirmed in Peru. It was further pointed out, however, that the educational climate in which women make decisions about family formation influences their fertility and the effect of their own schooling on fertility. The level of education of a community serves as an indicator of the diffusion of information and relative openness of residents to new ideas. Thus, the negative effect of education on fertility is enhanced when the women reside in communities where education is at a medium level rather than when they live where educational levels are low. For example, Mexican-American women living in areas in the U.S. with lower percentages of Spanish-surnamed residents have lower fertility and show sharper fertility declines with rising education. A study of the contextual effects of farm experience on the fertility of women born in the U.S. between 1901 and 1910 indicates that couples without a farm background exhibit relatively strong fertility differentials by socioeconomic status. Moreover, among urban residents it was found that farm living before marriage did not affect fertility. However, a strong effect was observed for urban residents who had some farm living after marriage.

The pervasive changes which U.S. marital patterns have undergone during the past decade contribute to the social framework which may affect future fertility. A longitudinal study in the U.S. found that rates of first marriage and remarriage have fallen sharply and divorce has increased. The vast majority of Americans continue to believe that marriage and family life are important. Nevertheless, the position of marriage relative to single life has changed. Most Americans no longer regard married life as necessarily better than singleness, nor do they hold negative views towards those who eschew marriage. Trends from several European countries are similar to those in the U.S. The study also found a trend toward less traditional sex roles, and, in 1980, 18-year-old daughters were less traditional than their mothers. It is probable that investigators will give more attention to the effects of changing marital patterns on fertility.

A major emerging pattern in fertility research has been the delay of childbearing, the rapid increase of first births to women over 30. This postponement of births at younger ages may be due to such factors as increased female labor force participation and housing. An investigator has found that wife's education has a significant positive effect on age at first birth in ten of fifteen countries. Factors relating to having a child quickly after marriage include young age at first marriage, lower education, non-use of birth control, large number of siblings, and no labor force participation. In addition, there has been an increase in the proportion of women who remain childless reflecting, perhaps, the modernization of sex role attitudes and the increasing legitimacy of singleness as an alternative life style. It appears that the majority of wives and husbands are keeping up with changing mores since each accurately perceives the partner's desired family size. However, a minority of husbands have inaccurate perceptions because of their stereotypes of the family size desires of women in general. It was also found that wives and husbands tend to have different views on the purposes served by their children.

A number of studies have been concerned with the mechanisms involved in fertility decline. A study of U.S. fertility in 1900 indicated that little effort was made to control fertility until desired family size had been achieved, and that the cost of educating children into the late teens was the factor most consistently related to the development of low fertility. In an historical study of fertility in rural Germany it was shown that fertility declines were due mainly to attempts to stop childbearing after reaching a target family size, rather than by extending birth intervals. This study also found that couples with less child mortality were more likely to practice family limitation, while greater experience with child mortality seems to have impeded such efforts. An analysis of Mormon genealogies over the last 100 years demonstrated that the fertility declines could be explained only through the adoption of contraceptive methods.

Motivations concerned with wanting children, as well as the use of contraception, sterilization, or abortion are important to the regulation of fertility. A study of women born 1901-1910 demonstrates that the proportion of births reported as unwanted increases progressively with order of birth. There was little difference in the wantedness of the first and second births, but for third and higher order births, the later a birth occurred the more likely the birth was reported as unwanted. An investigator finds that the percentage of marriages involving premarital births is increasing; most such births are probably unwanted. A study furnishes evidence that the attitude during pregnancy of "unwantedness" is significantly associated with an unfavorable pregnancy outcome such as short gestation, low birthweight, perinatal mortality, and presence of congenital

anomaly. An investigator finds that the prevention of unwanted births in at least nine countries could significantly reduce marital fertility. A study provides support for the thesis that there is a stable preference in contemporary United States for a family of exactly two children. An investigator reports that college students consider a limited number of options in making decisions about childbearing. Forty percent said that they had always assumed, without much deliberation, that they would have children, while 60 percent said they had thought consciously about having or not having children. There is more certainty in the woman's decision not to have a child (or another one) than to have one.

It is important to understand the factors involved in the effective use of fertility regulation. A study indicates that factors involved in choosing among contraceptives are: (1) being sure of avoiding pregnancy; (2) using a birth control method that lets husband and wife control when they have children; (3) avoiding major health problems that result from using a method; (4) utilizing a method that is easy to use; (5) avoiding having the method affect the wife's mood; and (6) avoiding birth defects. An investigator reports evidence which indicates that variation in contraceptive failure rate may be described by four factors: method, intention, age, and income.

Several analytical studies of the components of effective fertility regulation are in progress, and are paying special attention to less-studied and high risk groups. One investigator is examining a population of white, Hispanic, and Black females, and another is studying unmarried women between the ages of 20-29. A study of factors affecting the contraceptive practices of black couples is also in progress. These investigators will be providing findings by 1983 and 1984.

Voluntary contraceptive sterilization is being increasingly used in the U.S. and around the world to prevent childbearing. A study of the psychosocial and physical results of tubal ligation is in progress. Preliminary results indicate that women using tubal ligation, as compared with those not planning sterilization and those whose husbands have vasectomies, have the largest proportion of non-users of contraception, are least satisfied with their maternal role, have a slightly higher number of children, the greatest number of accidental pregnancies, and are most certain of the decision to terminate childbearing. This interesting study will be providing more findings which will increase understanding of factors involved in the voluntary sterilization of women.

An investigator reports that there is a considerably higher psychiatric admission rate for separated, divorced, and widowed women having abortion or carrying to term. This suggests that special provisions should be made to counsel women separated from their partners and seeking termination of a pregnancy originally conceived in an intact relationship.

Consequences of Family Size

Study of the consequences of family size continues to form a critical portion of the social and behavioral sciences program. An important reason for this is that the consequences of having one or more children is an important factor determining fertility. Clearly, understanding the determinants of fertility cannot be complete without taking into account the impact of consequences of fertility. This year, studies of the consequences of family size have focused mainly on low fertility (the effects of childlessness and one-child families) on the adults and children involved; on the economic costs and benefit of children to their parents;

and on the overall effects of family size on adults and children on several major dimensions of their lives.

The program focus on low fertility has been necessary because it is increasing, because very little research has been done on the consequences of low fertility, and because there are clear indications that anticipated negative consequences of childlessness or having one child is a definite motivational force for having a larger family size than a couple might consider ideal.

Several completed studies of only children have shown no adverse effects of being an only child. Only children were found to be more like firstborns in larger families, and were shown to be slightly superior on cognitive abilities and achievement to children with siblings. One study shows that "only" girls exhibit greater sex-role flexibility than other children (including "only" boys). On the whole, however, "onlies" simply have not been shown to differ from children with siblings on a wide range of factors including physical development, use of medical care, behavioral and psychological factors, marital status, number of children they had, divorce rates, occupational choice, or levels of income. A study which compared "onlies" with children with siblings in one-parent households also showed no negative results of being an "only." Two projects have completed in-depth studies of adolescent only children, comparing them to first and lastborns in larger families. These studies are concerned with the consequences of being an "only" on intelligence, interpersonal orientation, attitudes, time use, reciprocal interaction skills, and ego identity formation. They show only children and lastborns of two-child families score no lower on intellectual ability than firstborns of two-child families. Onlies were not rated as possessing less desirable personality characteristics; did not demonstrate lowered sociability; nor did they differ on adolescent developmental measures. Parents of onlies spent no less time in child-oriented activities than other parents. The importance of the family for adolescent development for both only children and others was paramount and rather surprisingly was found to be considerably more important than peer influence.

Several studies have been completed which concentrate on the consequences of both involuntary and voluntary childlessness. These studies looked at the effects on men, women, and married couples at different points in the life cycle and assessed the relationship of childlessness to educational and occupational attainment, social and economic well-being, measures of personal and marital satisfaction, and indicators of quality of life. One completed study shows that there is a continuum and no clear demarcation between the voluntarily and involuntarily childless on several factors. This in-depth study identifies several factors that affect strength of desire for children and also notes that there is a cohort difference in factors contributing to attitudes toward childlessness. Couples in the 1970s perceive childlessness as a more acceptable option and deal with it more openly and directly than do those from earlier cohorts. Another study shows that shifts in attitudes regarding childlessness are marked, with 84 percent of couples in 1962 believing that almost all couples who can should have children, whereas only 43 percent held this opinion in 1980.

A recently completed study shows the decision to remain childless has crucial implications for marriage role relationships. This study shows the "negotiating" advantages in a marriage increase for the wife the longer and more consistently she works, while the advent of a child acts as a barrier to achieving a fundamentally egalitarian marital structure. Less marital satisfaction for the wives was found in the traditional relationship than in childless marriages in which the

wife has career success. Another completed study shows childless couples to have a similar pattern of friendship and leisure to couples with children. A study of childless older married men showed that fathers and childless men have similar levels of well-being.

Studies on the economic costs and benefits of children have been undertaken to help examine the factors involved in one of the most critical determinants of family spacing, timing and size. Four studies are nearing completion on the economic consequences of family size. One shows that after two children and at a middle to low income level, family level of living goes down with increased family size despite the common phenomenon of parents working longer hours and more days of the year to increase income. At lower levels of income sacrifices may even be made in quality of food consumed (e.g., more starches and less protein) as family size increases. Preliminary findings on studies estimating actual expenditures on children show that the cost of children is a sizable component of the average American family's expenditure stream. A boy, born to a father aged 25, will (in 1981 prices) be responsible for family expenditures of about \$62,500 during the first eighteen years of life. Expenditures on girls are approximately the same total, however the commodity distribution of expenditures on boys and girls differ. For example, 25 percent of total expenditure on a boy is for food while it is only 22 percent for a girl. Clothing expenditures are higher for girls, and transportation higher for boys. Examining the level of expenditure by age of child, it was found that senior high school students account for about 30 percent of total expenditures, and infants 15 percent. The years age 3 to 13 are the lowest cost age periods. These studies will have considerably more detailed findings on expenditures in families of various sizes, income, ages, place of residence, and occupation.

Six new studies are underway to determine the consequence of family size on the changing roles of women and men. They are addressing the effect of children on use of time, on changing educational attainment for the parents, on wages earned and foregone and shifts in types of activities by both parents. The impact of sex-role changes on time allocation is being studied. In addition, values are being assigned to nonmarket activity of parents in both intact marriage and single-parent parent households varying in income, age, family size, education, residence and occupation.

A study of the consequences of childbearing on older men has found that the number of children had no affect on fathers' well-being or satisfaction with children. However, men with all sons had significantly lower well-being, higher depression and higher loneliness/dissatisfaction scores than did men with all daughters, and somewhat greater depression than did men with children of both sexes.

A critical review of the literature on the effects of family size is underway. Preliminary findings are consistent with earlier work showing that members of smaller families fare better than members of larger families across a broad range of life outcomes. There is particularly strong evidence that children from smaller families are advantaged with respect to intellectual performance, academic achievement, and, as adults, occupational prestige, even when their social class of origin is controlled. In the past decade there has been considerably more interest in the effects of family size on parents, and this work also tends to favor small families. Research on family size since 1973 is characterized not only by increased methodological rigor, but also greater theoretical development--leading to greater confidence in the strength of the findings.

Adolescent Pregnancy and Childbearing

Concern about early pregnancy and childbearing revolves around the effects on the young woman, her child, the child's father, and other family members involved, as well as society as a whole. While birthrates of older adolescents have declined in recent years, birthrates have increased and then decreased among younger adolescents. There has been an increase in the likelihood of out-of-wedlock births, and adolescents still account for one-third of the legal abortions performed in this country each year. There is substantial evidence of high levels of unintended pregnancy and childbearing among adolescents, and research is generating an improved understanding of the effects of this behavior. In previous years, the effects of childbearing on children's early and school age development as well as the adolescent's educational, occupational, fertility and marital experiences have been reported. Effects on the fathers and other family members have also been addressed. The research reported in 1982 has provided insight into four major areas within the broad topic of adolescent pregnancy and childbearing: 1) the economic impact on society; 2) the impact of sex education on adolescent sexual activity and pregnancy; 3) the role of the adolescent couple in decision making regarding contraception and pregnancy resolution; 4) the role of the adolescent's family in determining sexual activity, use of contraception, pregnancy, decision making regarding pregnancy resolution, and assisting in child-rearing after the baby is born.

Early childbearing has an economic impact on society. When it prevents individuals from achieving their educational and occupational goals, society loses their contributions to the economy and the tax base. Research in previous years has documented that the adolescent mother never catches up to her peers who are not teenage mothers in the areas of educational and occupational attainment.

More directly, if early childbearing leads to greater use of public services, there is a direct impact on public expenditures. These public sector costs include Aid to Families with Dependent Children (AFDC), Medicaid, food stamps, foster care, and so forth. A mother's age at first birth has only a weak direct influence on whether or not an AFDC family receives Food Stamps, which depends primarily on the overall composition of the household. Mother's age at first birth exerts a negative indirect effect on the amount of the Food Stamp bonus, primarily through the larger number of children. A mother who had a first birth at a young age is likely to have more children and therefore receive a larger Food Stamp bonus. The question arises as to how much could be saved if some of the adolescent births were delayed. The net effect of a one year-increase in welfare mother's age at first birth generates an estimated saving of about \$56 million in Food Stamp costs. Mother's age at first birth is found to affect duration of AFDC payments with a total impact of about 2.7 months shorter current duration for each year's postponement in the age of first birth. The AFDC cost savings from shorter duration are estimated as \$873 million, in 1975, from a one year increase in age at first birth.

The research findings of this year and previous years show the enormous costs of adolescent pregnancy and childbearing for the young mother, her child and society. These serious consequences suggest the benefits of a policy which would intervene and lead to the delay of many of the adolescent births. Such a policy, however, could be expected to be effective only if solidly based on knowledge about the determinants of adolescent childbearing. Research on the determinants of teenage

pregnancy and childbearing has included studies of individual, couple, familial and societal level factors affecting adolescent behavior. One area of research has focused on adolescents' knowledge about reproduction, their knowledge about and use of contraception and the role of sex education in providing the information. A national survey found that about three-quarters of young men and women living in metropolitan areas of the United States have had sex education in school, and about eight out of 10 of those who have taken such a course report that they received information about different types of contraceptive methods. About three-quarters of students who have taken a course say that they were taught something about where contraceptive methods can be obtained or about the possible side effects of the various methods. Concern has been expressed about whether or not sex education would lead to increased adolescent sexual activity, yet research findings indicate that young people who have had sex education are no more likely to have had sexual intercourse than those who have never taken a course. However, sexually active young women who have had sex education are less likely to have been pregnant than their counterparts who have had no such instruction. Data from a 1979 survey show that teenage women who have had sex education are somewhat more likely to have practiced contraception at first intercourse than are those who have not had a course. Black teenage women, but not whites, who have had a course that provided information about different types of contraceptive methods are more likely to ever use (prior to pregnancy or survey) a prescription method and a higher proportion of all teenage women who have had such instruction report ever-use of any method than of those who have never had such a course.

Information about reproduction and contraception is provided not only through sex education courses in school but also at the clinics where teens obtain contraceptives. Studies in clinics show a surprising lack of knowledge among adolescents even when the information has been presented to them. Only somewhat over half of the females in a Chicago teen clinic sample had correct knowledge about contraceptive methods. Sixty percent of the males knew less than their partners. Females retained less than they were taught in the clinics because the information was too abstract and they were often too anxious and distracted to learn the new material. The males felt relatively powerless to control fertility since most of the recommended methods were for females.

Although adolescents may have information presented to them about contraception, other factors intervene to prevent many teens from obtaining and effectively using contraceptives, such as their perceptions of the medical care system, lack of motivation, and insufficient interaction with their partners. Major findings related to adolescents' perspectives of the medical care system and use of the system for contraceptive purposes can be grouped according to parent-related issues, such as fear of discovery and reluctance to reject parental values overtly, and thoughts and feelings about doctor-teen interactions. These concerns are heightened when teens seek reproductive system care. The ambivalence of teens about parental influences on their medical care is demonstrated by their frequent mention of the importance of parental approval and support while concurrently stressing their interest in establishing an independent relationship with the physician. Since the key factor for teens is the risk of others, especially parents, discovering their use of birth control, confidentiality becomes paramount and their evaluations of a doctor's trustworthiness on this matter can determine whether they visit the doctor for contraceptives. The need to enhance teens' comfort and ease their embarrassment is critical. The offering of information is preferable to the questioning of the teen. A nonjudgmental, matter-of-fact presentation which stresses confidentiality is most valued.

In examining communication and decision making regarding contraception among young unmarried couples, it was found that the couples who were best protected were ones in which one partner took charge of contraception, rather than having the responsibility shared. On the other hand, couples whose overall communication was high tended to be effective contraceptors, suggesting that individuals determined to avoid a pregnancy may use communication more as a negotiating device to persuade partners that contraception is necessary than as a problem-solving device, to jointly select contraceptive methods.

The impact of the family in determining adolescent sexual activity, contraception, pregnancy, and childbearing has been examined. While socioeconomic characteristics of family (mother's education, current and past labor force involvement, and job status, as well as father's education and occupational status) are not associated with rates of sexual intercourse, the sexually active daughters of higher status parents are somewhat more likely to use contraceptives at the time of first and subsequent intercourse, lowering their rates of pregnancy. The composition of the teenager's family is highly important. Rates of sexual intercourse and pregnancy are significantly higher among teenagers whose parents are not currently married, who have a large number of brothers and sisters, and who have one or more sisters who are teenage mothers. Girls who report that their parents closely monitored their early dating behaviors have significantly lower rates of sexual intercourse and pregnancy. Controlling for family background characteristics, the educational aspirations and work experiences of teenagers have limited effects on their rates of sexual intercourse and pregnancy. These family factors account for most of the intercourse and pregnancy rate differentials observed between Blacks and non-Blacks in the city of Chicago.

Another study found no differences between contraceptors and noncontraceptors in terms of family structure, education and employment, and whether the mother had been an adolescent when she first had a child. Mothers' involvement in the sexual socialization of daughters influences contraceptive knowledge and use. While mothers show high levels of such involvement with girls, fathers show low levels for both sexes. Girls were found to be better informed than boys concerning contraceptive effectiveness, and the risk of pregnancy.

Other studies have examined decision making regarding the resolution of pregnancies. Few adolescent pregnancies are intended. Most of the unplanned pregnancies are also unwanted. Although most respondents became pregnant within a steady, ongoing relationship, in which the couple had known each other for a long time, about a third found being pregnant a crisis, in part because they lacked support from their partner. Others felt stigmatized by being pregnant. Only 11 percent said they were pleased to be pregnant. When they first thought they might be pregnant, 82 percent talked to someone about their suspicions, and about two-thirds talked to their partner. Once respondents knew they were pregnant, all talked to someone about the situation, and 96 percent talked to their current partner. Two thirds of the pregnant girls reported having contingency plans before they got pregnant. Those who lacked contingency plans were of two distinct types: (1) some had been using birth control and felt safe, but stopped unexpectedly and temporarily; and (2) most others felt "magically protected" and believed "It can't happen to me."

Investigating a series of social, behavioral, attitudinal and emotional variables in relation to the choice of delivery or abortion of pregnancy, there were significant differences in experience and perceptions of economic and educational

factors. More adolescents who delivered were below grade level in school, had poor or failing grades, had no plans for post-high school training or education, had fewer parental expectations for post-high school training or education and did not think a baby interfered with their educational plans. Girls who delivered were less likely to have ever had a paid job, less likely to identify any future job, and more likely to receive welfare.

The most important consideration for those who chose abortion was not letting plans for the future be disrupted. They also wanted to keep people from knowing they were pregnant, to protect their parents, to do what was best for their boyfriends, or to be able to finish school and get a good job. A few also worried about what would be best for the child. Those who decided to keep the child, on the other hand, were most concerned about what was best for the child. Their peace of mind was also critical. Many felt that abortion was murder and something they could not live with, no matter how punishing it was to have a child at this point in their lives. About half also were concerned about their relations with their partner. Both groups were quite realistic about the impact of a child on their lives.

More adolescents who delivered perceived their mothers and fathers as clearly supportive of the pregnancy. They also had more support from the boyfriend and girlfriends and had more girlfriends who had babies. These delivery and abortion groups were matched on age (14-17 years), race (Black), and marital status (never married). All were low income and from the same urban residential area. They did not differ in measures of self-esteem, sex-role attitudes or nine emotional factors including depression, anxiety and hostility. The delivery group had less contraceptive information than the abortion group, although both groups had low scores on this measure.

The impact of an adolescent pregnancy and birth continues not only on the adolescent herself, but also on her family and sometimes on the baby's father and his family. One study with a sample including both adolescent mothers and adolescents who delayed a birth, examined the family context of adolescent parenthood. The investigator studied the adolescent's relationships within the family of origin as well as with the baby's father and his family, and the adolescent's expectations regarding her own future marriage plans. The study corroborates the trend towards less traditional attitudes concerning premarital pregnancy, e.g., more adolescents felt they may never get married, yet believed having a child out of wedlock did not hurt their chances for marriage. Their behavior reflects these attitudes; in the sample, marriage was far less likely to follow premarital conception.

Generally, the families of pregnant adolescents report a sense of renewed happiness and cohesion following the pregnancy. However, observation of their interactions show the family's perceived "honeymoon" in the period surrounding the birth is followed postpartum by disillusionment and distress. The adolescent childbearers appeared significantly more depressed for an average of 11 months postpartum when compared to delayed childbearers. Although the adolescent childbearers and their families show various styles of coping with early parenthood, generally the adolescent is more likely to see her mother as more controlling, dissatisfied with her, and less affectionate than she did before the birth of the child. The percentage of families receiving public assistance or AFDC likewise increased after the third trimester of pregnancy, with conflict between the adolescent and parents often being about money.

In general, there are problems between the adolescent mother and the baby's father following the birth. Approximately half report feeling less close to him. Their expectations of his providing financial assistance postpartum are not borne out. In terms of his family, his relatives were generally uninvolved in prenatal planning. In almost half of the cases there is no contact with his family at all. Findings suggest that the adolescent may be caught in the difficult bind between her own family and the baby's father and his family. This continues to be the case after the baby's birth.

Migration and Population Distribution

While birth and death rates are the major determinants of national population size and age composition, the movement of people is the important third side of the demographic triangle. The growth of the U.S. population will likely be increasingly influenced by the movement of people from other countries, and specific states such as California, Texas, and Florida may be flooded with both migrants from other states and from abroad, with the resultant impact on health and other services. The new and powerful forces governing population movement to and within the U.S. have combined to pose population problems and scientific questions. NICHD supported research has focused on the determinants and consequences of how a population changes through migration. Family change such as the birth of a child or divorce plays a strong role in decision making regarding mobility to adjust to the new equilibrium.

Overall rates of migration within the U.S. declined between 1966 and 1976 for both whites and Blacks. Higher overall migration rates of young white males as compared to young Black males is due to repeat migration. For previous migrants the migration rates for all age groups were considerably higher for whites than for Blacks, e.g., 23 percent vs. 15 percent, respectively, after two years. During the 1970s, city-to-suburb residential mobility continued much higher for whites than Blacks but increased markedly for Blacks.

Projected population movements for several of the nation's largest Standard Metropolitan Statistical Areas (SMSAs) do not portend any significant shift from suburbs to central cities. On the contrary, population projections of a declining metropolitan area (Pittsburgh) and a growing one (Houston) over the years 1970-2000 suggest that both SMSAs will likely sustain significant city-to-suburb redistribution. The projections affirm that in the long run central city population change depends more heavily on the capacity of the entire metropolitan area to attract inter-labor market migrants than on the capacity of the central city to attract intrametropolitan residential movers. Moreover, population projections of Detroit, Atlanta, and Houston, based on a model which incorporates both types of moves, support a continuing city-to-suburb movement. Census data also suggest that neither the earlier propensity (1955-1975) to choose a central city destination nor trends toward smaller, childless and primary individual households will yield a significant increase in the household populations of declining central cities.

Within SMSAs, neighborhood identification has a strong structural basis in the status and family composition of the area and also in their relationship to the central business district. Most urbanites perceive the metropolis as a series of non-overlapping discrete communities. From 1929 to 1979 the purely social function of neighborhoods declined noticeably. The best predictors of local ties

are measures of social and financial investment in the locality, the presence of children and long-term residence.

A study of foreign students in U.S. universities indicates that per capita income in the country of origin is positively and significantly related to flows of undergraduates but not of graduate students. The price of U.S. higher education to foreign students is negatively related to flows of both undergraduate and graduate students. Opportunities for higher education in the country of origin are inversely related to demand for U.S. undergraduate education. Except for a few countries, the data suggest that immigration is not a strong explanation of foreign student demand for U.S. higher education. With respect to the immigration of professional manpower, 1969 data indicate that direct professional immigration is very positively related to the ratio of U.S. wages or income to those in the country of origin. Indirect professional immigration (foreign student adjustment of visa status) is also positively related to an earnings ratio but is negatively related to the difficulty encountered in adjusting visa status.

A study of the migration and adjustment of migrants from a rural, developing country region (the Philippines) to the major urban area of the country (Manila) and to an important U.S. destination city (Honolulu) shows that migration decisions are based on a complex set of familial and quality of life considerations and are not dictated simply by economic circumstances. In fact, household and family strategies carry more weight than individual desires in reaching decisions about migration. Out-migrants often maintain substantial obligations and contacts with their previous household through monetary remittances, visits and correspondence. The study has also confirmed the importance in decision making of assistance from relatives and friends in different potential destinations.

Two Mexico communities studied differ substantially at the community level but have similar underlying patterns of sending migrants to the U.S. Both have developed a tradition of out-migration, both legal and illegal. However, one town is dominated by a legal migrant elite that moves seasonally to the United States, while the other is dominated by a migrant elite that maintains extensive ties with daughter communities of legal migrants in several U.S. cities.

The decline in the rate of natural increase in the United States has led to an increased proportion of annual population growth due to the net number of immigrants and their fertility and mortality levels. The focus here is on fertility, since the mortality of immigrants on balance is probably similar to that of the native population (with higher death rates in the developing countries of origin being offset by a younger age distribution of immigrants). Three NICHD supported studies compared immigrant and native U.S. fertility.

Female immigrants to the United States are a heterogeneous group with respect to fertility. Their fertility levels range from much above those of the native-born population to fertility at or below native levels. Country of origin, length of stay in the U.S., and citizenship status have important effects on the fertility of foreign-born women, and socioeconomic variables are inversely related to fertility. Women from one sending area, Mexico, have fertility higher than that of native U.S. women.

A 1980-81 interview study of Mexican-origin parents in Los Angeles found that 46 percent of births were to undocumented mothers, 25 percent to mothers who were either legal residents or naturalized citizens, and 29 percent to mothers of

Mexican origin born in the U.S. At least 13 percent of all births were to undocumented mothers where either the mother or the father was of Mexican descent. There were marked differences in educational attainment, ability to speak English, and income between parents of Mexican descent born in the U.S. and undocumented parents from Mexico. Parents who were legal residents or naturalized citizens of Mexican origin were intermediate.

A substantial proportion of undocumented parents received benefits from various entitlement programs. For certain programs such as AFDC (Aid to Families with Dependent Children), food stamps, and Medicaid, American-born children of undocumented persons are legally eligible, but the receipt of payments by undocumented persons for unemployment compensation is clearly outside the law. About 19 percent each of Mexican-American mothers born in the U.S. and of undocumented mothers received food stamps as compared to 16 percent of legal residents or naturalized citizens. Furthermore, among fathers in the U.S. who worked part of 1979, the proportion receiving unemployment compensation payments was 19 percent for legal residents or naturalized citizens, 14 percent for the undocumented, and seven percent for those born in the U.S. However, among those receiving benefits from various entitlement programs the amount received by the undocumented was less than that received by legal residents or native-born citizens.

Analysis of 1970 census tapes demonstrates that wife's education among Mexican Americans is inversely related to both current and cumulative measures of fertility among all cohorts. First-generation Mexican-American women exhibit lower cumulative fertility than other Mexican-American women, but lower recent fertility only for the youngest age group, suggesting that immigration reduces fertility, either through postponement, spouse separation, or interruption. Third or higher generation women show slightly lower fertility than second-generation women.

An interview study of both undocumented Mexican workers and Chicanos at work sites in San Antonio and Austin, Texas found that San Antonio provides broader work opportunities in the manufacturing sector. Interviews in Austin affirm that family migration is a significant component of the migration of Mexican undocumented workers to the U.S. Undocumented workers in San Antonio have fewer problems in obtaining health services than do those in Austin. Analysis of social network patterns indicates a significant separation between the undocumented and the Chicano community on the dimensions of work, culture and social interaction.

One project studied West Indian workers who migrate seasonally to southern Florida to harvest sugar cane. Of the all-male labor force, 82 percent came from Jamaica; the rest from the Eastern Carribean. Average age is 34.5 years; the vast majority are farmers from large households (6.1 persons on the average) and have little education (under four years of schooling on the average). Of the net seasonal wages from cutting cane (about \$3,000), 23 percent are remitted to the islands via an obligatory savings plan (\$500-\$600 per worker), as purchases (\$530), and in cash. Resources transmitted are used primarily for the support of the worker's household rather than to accumulate productive assets or to enhance agricultural output.

Workshops

Three workshops were held for the purpose of bringing together contractors and grantees who are funded on the topic of each workshop to give them the opportunity

to discuss with one another and with the staff of the Branch their aims, progress, methodology, areas of mutual interest, and current or anticipated problems.

- 1) Implications of International Immigration for the U.S. (November 16-17, 1981)
- 2) Effects of Fertility on the Changing Roles of Women and Men (March 19, 1982)
- 3) Family and Household Demography (May 17-18, 1982)

Conferences

The Conference on Delayed Childbearing--Trends and Implications was held on September 17-19, 1981.

A conference on Methodology in Fertility Research is to be held in September, 1982. The purpose is to discuss the state of the art and identify areas where new methodology is needed as well as areas where specific types of methodology should or should not be used.

Targeted Research

Requests for Contract Proposals (RFPs)

A Sources Sought Announcement: Request for Qualifications Statement (Synopsis No. 82-) was issued to determine whether organizations other than Princeton University have the capabilities and resources required to collect and annotate bibliographic data currently published in the quarterly Population Index and entered into POPLINE, a computerized data base of the National Library of Medicine. Population Index has been published by Princeton since 1935; the collection and annotation effort has been supported by NICHD as a research resource since FY 1971. If realistic competition is found, an RFP will be issued in FY 1983.

A research initiative entitled "The Consequences of Changing Family/Household Structure" will be initiated in late FY 1982. This program of research will focus on the consequences to society and to individuals of the radical changes in the American family and household that have been documented through past efforts. This program will examine how socioeconomic status, health, and mental well-being are affected by these patterns of change and also how households relate to one another to strengthen their family relationships. The program of research will examine the relationship of critical demographic events, such as birth, death, marriage, divorce, and migration to the structure and function of the family and household. Special attention will be placed on how these interrelationships affect child care arrangements, health status of individuals, living arrangements, migration decisions, and the breaking away of dependent children from the parental household.

Interagency Agreement

An interagency agreement was undertaken with the U.S. Bureau of the Census to produce a computer data tape containing an updated version of the book entitled, "Fertility Tables for Birth Cohorts by Color: U.S., 1917-1973." These data would be updated through the year 1980. The data tape would be made publicly available in FY 1983.

The Branch has entered into an interagency agreement with the National Center for Health Statistics to support partially the National Natality Follow-Back Survey of 1980 as an important resource for fertility, perinatal and mortality research. A public use data tape would be available late in fiscal year 1983.

The SBSB entered into an interagency agreement with the Department of Labor to add fertility and child care questions to DOL's ongoing National Longitudinal Survey of Labor Force Behavior--Youth Survey. A public use data tape containing the entire Survey will be released in September, 1983.

An interagency agreement was developed with the Center for Disease Control was entered into to collect data in Puerto Rico on fertility, family planning, and a variety of social, demographic and economic factors associated with fertility. A public use data tape will be released in January, 1984.

In June 1982, the Current Population Survey was supplemented through an interagency agreement with the Bureau of the Census to collect data on fertility expectations and child care. A public use data tape is expected to be released in December 1982.

SBSB has entered into an interagency agreement with the National Center for Health Statistics to collect data on the contraceptive practices and unwanted childbearing among women 30-44 in Cycle III of the National Survey of Family Growth. The Survey is expected to go into the field in 1982.

Program Announcements

A program announcement was issued on October 9, 1981, on the topic of "Effective Fertility Regulation" inviting grant applications for the support of research on the effective/ineffective use of contraceptives, especially for groups who have not been extensively studied.

A program announcement was issued on April 23, 1982, to request research on four targeted areas.

- 1) "Antecedents of Risking Unintended Pregnancies" invited research on the relative strengths of biological, demographic, psychological, social, cultural and other factors which interact as antecedents of unprotected sexual relations. Research was intended to develop findings and test theories and implications for the prevention of unintended pregnancies.
- 2) "Consequences of Pregnancy Losses for Adolescents." This research was intended to evaluate the relevant factors which interact to contribute to the psychological, social, health and other consequences of pregnancy losses for adolescents.
- 3) "Adolescent Childbearing and the Family." This announcement focused on the role of the adolescent's family in influencing fertility-related behavior and the effects of that behavior on the family.
- 4) "Prevention of Adolescent Pregnancy." This announcement was aimed at the development of theories and evidence to provide a basis for the prevention of adolescent pregnancies.

SBSB is to issue a program announcement on the "Adjustment of Recent Migrant Groups to the U.S." Requested research is to focus on the characteristics and impact of recent migrant groups, such as Cuban and Haitian entrants, including economic contributions, social adjustment and assimilation, and requirements for, and use of, health and other services.

A program announcement is to be issued with the title, "Research on Perceived Cost and Value of Children." The research suggested will follow previous research on actual expenditures and opportunity costs of children. Since perceived costs and values affect fertility decisions (timing, spacing and number of children), research research will be encouraged to describe them and and to compare them with actual costs.

A program announcement designed to encourage "Research on Strength of Motivation for Fertility Behavior" will focus on determinants of fertility behavior through in-depth, psychological studies aimed at assessing the strength of the positive and negative forces affecting such behavior.

Institutional Programs in Multidisciplinary Population Research

The SBSB supports three kinds of Institutional Programs in Population Research at major U.S. institutions. Support for these institutional programs enables coordinated, highly skilled groups of behavioral-social scientists in a variety of disciplines to organize and conduct multidisciplinary population research programs. These programs are designed to attack complex population problems that cannot be adequately studied by an individual investigator working alone.

- A. Population Research Centers (A Population Research Center grant provides for centralized services and facilities required for enhancement of the quality and productivity of existing population research projects.)

Population Research Centers supported by SBSB, together with their major research areas, are located as follows: (1) University of Wisconsin at Madison--demography and human ecology; (2) University of Texas at Austin--demography of minority groups, households, and labor force, and population change and distribution; (3) The Johns Hopkins University--demography, teenage fertility, and reproductive biology; (4) Princeton University--demography, population economics, and statistics; (5) University of Michigan--fertility and family planning, population distribution and differentiation, and economic demography; (6) University of Pennsylvania--fertility, population movement, and economic demography; (7) University of North Carolina--fertility, family planning, migration, and population statistics.

- B. Specialized Population Research Centers (Specialized Population Research Center grants provide for the support of a comprehensive population research program that is specifically responsive to research areas specified by the CPR.)

The SBSB is funding two Specialized Population Research Centers. The Center at the Rand Corporation, Santa Monica, California, has two major foci: (1) the demography of families and household and (2) regional and local population changes. The Center at the National Opinion Research Center in Chicago specializes in the economic demography of the family.

Population Research Manpower Development

NICHD awards grants for the support of institutional behavioral-social population research training programs, behavioral-social predoctoral and postdoctoral trainees, research career development of individuals with outstanding potential for independent behavioral-social population research, and senior postdoctoral fellows.

A. National Research Service Awards--Institutional Research Training Programs

During fiscal year 1982, NICHD supported 12 behavioral-social population research training programs located at the following universities: Princeton; Wisconsin (Madison); Michigan, Economic Demography and Population and Human Ecology; Brown; Texas (Austin); Florida State; Pennsylvania; Yale; Chicago; North Carolina, Population Studies and Population Statistics.

B. Other Awards and Fellowships

Three behavioral-social postdoctoral fellowships, two Research Career Development Awards, and one Senior Postdoctoral Fellowship were awarded during fiscal 1982.

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Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Fertility Values and Family Growth
Contract Number : N01-HD-62834
Contractor : Temple University
Money Allocated : \$180,753 (1976); \$30,049 (1978)

Objectives: This project examines the developmental effects of actual fertility on fertility values within religious and SES subgroups. A previous study indicated that the experience of bearing children was related to people's perceptions of a range of values related to fertility and family size desires. However, because longitudinal data were not available, it could not be determined whether people with three children had different values from those with no children because of the presence of children. The study proposed here will establish more clearly: (a) the effects of parity increase on the relationships of fertility values to desired family size; (b) the fertility value relationships that are associated with Catholic/Protestant affiliation, social class and those that are independent of these two factors; and (c) the parental experiences associated with an increase in parity.

Major Findings: Preliminary analyses of cross-sectional data produced a number of tentative conclusions which will be further tested when longitudinal data is available. Generally, the perceived costs of children are more related to family size desire than are the perceived benefits of children. Anticipation of the rewards of children were most important for the initiation of family building and recognition of costs of children were most important for the decision to terminate family growth only for upper status Protestants. The importance of the arrival of the first child in changing perceptions about childbearing is evident from two findings: (1) anticipated rewards of childbearing were found to be related to desire for larger families mainly for childless couples; (2) the proportion of respondents reporting unexpected problems when their (last) child arrived was significantly greater among women with only one child than among those with two children. However, the arrival and experience of each child in the family altered the relationships between fertility values and desired family size. The satisfaction of child care and development was an important fertility value only among Protestants. Concerns about family interactions in the form of giving attention among family members was an important fertility value, although its prominence varied among social subgroups. Financial matters were a special fertility concern of the Protestants, particularly the lower status ones. Protestants differed from Catholics in their developmental pattern of expectations of and reactions to the consequences of children, but fertility values generally were little related to fertility desires among the Catholics.

Significance to Biomedical Research and Program of the Institute: This project will enhance our understanding of the process of family formation and improve our understanding of the consequences of family size by elaborating on how fertility influences future decisions about having children.

Proposed Course: The first stage of this project was completed in FY 80. The second stage is expected to begin in FY 83.

ANNUAL REPORT
October 1, 1981 through September 3, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Adolescents' Perspectives on the Health Care System:
A Determinant of Fertility
Contract Number : N01-HD-82837
Contractor : University of North Carolina
Money Allocated : \$105,786 (1978); \$108,120 (1979); \$58,225 (1980); \$9,274
(1982)

Objectives: The purpose of this research is to identify the nature and sources of adolescent women's perspectives on the established medical care system, and the impact of these perspectives on their use of the system for fertility-related services. The specific objectives are to identify the reasons why adolescent women may be reluctant to use the established medical care system for fertility-related services, and to assess the usefulness of various techniques for collecting data about adolescents.

Major Findings: Major findings related to adolescents' perspectives of the medical care system and use of the system for contraceptive purposes can be grouped according to parent-related issues, such as fear of discovery and reluctance to reject parental values overtly, and thoughts and feelings about doctor-teen interactions. The ambivalence of teens about parental influences on their medical care is demonstrated by their frequent mention of the importance of parental approval and support while concurrently stressing their interest in establishing an independent relationship with the physician. These concerns are heightened when teens seek reproductive system care. Since the key factor for teens is the risk of others, especially parents, discovering their use of birth control, confidentiality becomes paramount and their evaluations of a doctor's trustworthiness on this matter can determine whether they visit the doctor for contraceptives.

Teens want doctors to discuss health matters directly with them, to give thorough explanations of procedures and options, and to show a personal interest in them. Most teens agree that doctors should maintain a professional attitude, but show humor and flexibility. These aspects of the physician-patient relationship increase in importance when applied to reproductive health care. Here, the need to enhance teens' comfort and ease their embarrassment is critical. The offering of information is preferable to the questioning of the teen. A nonjudgmental, matter-of-fact presentation which stresses confidentiality is most valued.

Significance to Biomedical Research and Program of the Institute: Other studies have pointed to the high proportion of adolescent contraceptors who use clinic services, but little research has addressed adolescents' avoidance of the established medical care system. This system may be the only one large enough to meet adolescents' demands for family planning and related services.

Proposed course: The project was begun in FY 78 and expired in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Adolescents' Use of Information about Conception and
Contraception: Cognitive and Interactive Processes Among
Never-Married Female and Male Partners
Contract Number : N01-HD-82836
Contractor : Planned Parenthood Association of Chicago
Money Allocated : \$91,224 (1978); \$61,419 (1979); \$15,000 (1980)

Objectives: The purpose of this project is to determine the knowledge which adolescents have concerning conception, contraception, and sexuality and their use of that information in the context of their sexual, contraceptive, and pregnancy behaviors.

Major Findings: Over half of the females in this teen clinic sample had correct knowledge about contraceptive methods. Less than 10 percent of their male partners had correct knowledge and sixty percent of the males knew less than their partners. Females knew less than they were offered in the clinics because the information was too abstract and they were often too anxious and distracted to learn the new material. The males were rarely offered such information by adults and felt relatively powerless to control fertility, since the recommended methods were for females.

Having good understanding of conception and contraception were not associated with contraceptive use. Females used contraceptives consistently and properly when they understood that they could become pregnant. Almost one-half understood this personal fact before first intercourse or soon thereafter. Others persisted for variable lengths of time in the belief that, although sexual intercourse is related to pregnancy, this was not currently true for them. Following a pregnancy scare or a pregnancy they initiated proper contraceptive use. About ten percent of the females, despite repeated exposure to clinics and pregnancies, were unable to use contraceptives consistently and properly. All had exceptionally problematic family circumstances making attention to contraception difficult for them.

Significance to Biomedical Research and Program of the Institute: Adolescents' attitudes and knowledge concerning contraception is one of the central concerns of the Institute.

Proposed Course: This project expired in FY 81.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Research on the Determinants of Repeated Adolescent Pregnancy and Childbearing
Contract Number : N01-HD-82838
Contractor : Johns Hopkins University
Money allocated : \$52,752 (1978)

Objectives: This project uses the extant data base of a Johns Hopkins longitudinal research and service program established in 1973 for adolescent mothers to identify those young women who had a subsequent (unwanted) pregnancy and to compare them with matched controls who did not experience a subsequent pregnancy. The study, which included about 90 cases and an equivalent number of controls matched by race and age, analyzed data collected during the first pregnancy and at the four-week postpartum visit. The data available about mother, father, and pregnancy included: demographic, educational, and family background variables; contraceptive use; amount of prenatal education; and contraceptive prescribed postpartum. These objectives were to provide a broad and complete picture of the problem among the urban adolescents, gross indicators of risk of repeated pregnancy, and information about the outcome of subsequent pregnancy.

Major Findings: Preliminary findings indicate differences in characteristics of adolescents who experience repeated pregnancy, although they are in a program with a strong emphasis on prevention. The adolescents who became pregnant again appear to be younger, poorer, and less competent academically, and with lower levels of self-esteem. With respect to contraception, they tend to use less effective methods and to have more frequent method changes.

Significance to Biomedical Research and Program of the Institute: This research, requested under RFP 78-8 relating to "the determinants of adolescent pregnancy and childbearing," is central to the program of the Institute. The project's considerable value lies in the study of young people who create hardships for themselves and society--adolescents with repeat pregnancies. The research looks at individual characteristics as well as identifying the structural sources of repeat pregnancies.

Proposed Course: This project was initiated in FY 78.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Sociosexual Development in Black Adolescents within the Family Context: A Longitudinal Study
Contract Number : N01-HD-82840
Contractor : Howard University
Money Allocated : \$99,499 (1978); \$107,253 (1979); \$112,630 (1980); \$7,000 (1981)

Objectives: The purpose is to explore the effects of psychological adjustment, sexual knowledge and attitudes, family interaction, moral and ethical reasoning, socioeconomic status and environmental impact on sexual behavior. The project involves a five-year longitudinal study of 99 Black early adolescents and their parents. Periodic medical examinations, unstructured interviews using a variety of stimulus materials, and videotaping of family interaction are used. Participants are a volunteer nonrepresentative sample of healthy 10 year olds from low and middle income families, evenly split male and female. Test materials (pictures, incomplete stories and simulated taped conversations) are developed. Some family interaction observations are made.

Major Findings: In a study of 99 male and female preadolescents aged nine to 11 years, 86 percent of the girls and 89 percent of the boys reported that their main source of reproductive information category was another family member usually but not always the mother. Middle income males had the highest percentage of participants with accurate and complete reproductive information and low income males had the most participants with no knowledge.

The level of reproductive information was scored based on three basic content components, sophistication of language used and accuracy of the process described. Statistically significant correlations were found between higher levels of reproductive information and age of participant, income status and family structure. Older age, middle income status and single parent family structure were correlated in a positive direction. The relationship between biological maturation and reproductive information differed for boys and girls. The biologically mature female had a greater amount of information about reproduction, but the less mature male had more information than his mature peer. This inconsistency may be due in part to the greater number of girls as compared to boys who had their onset of puberty at this point in time.

Significance to Biomedical Research and Program of the Institute: This project relates to the Institute's concern with adolescent pregnancy and the concomitant psychosocial factors.

Proposed Course: This project expired in FY 81.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : A Study of the Consequences of Deciding to Remain Childfree,
Compared with Deciding to Have Children and Deciding to
Postpone Children
Contract Number : N01-HD-92805
Contractor : University of North Carolina
Money Allocated : \$71,425 (1979)

Objectives: This project analyzes consequences of remaining voluntarily childless. The voluntarily childless are being compared with postponers, undecided, and parents to test the hypothesis that voluntarily childless wives will be more likely to: (a) emphasize the costs of children, negative motivations for parents having children and positive motives for remaining childless; (b) be characterized by dyadic withdrawal; (c) have an egalitarian division of labor in the home; (d) have consistently high achievement for the wives; (e) have high marital satisfaction; (f) have higher combined income, less debt, and higher satisfaction with their standard of living. The study is also investigating whether voluntary childlessness is a qualitatively unique phenomenon or a quantitative extension of a model that explained low parity processes. Analyses are being performed on extant data from a random sample of 186 voluntarily childless and 598 other married women.

Major Findings: The decision to remain childless has crucial implications for marriage role relationships. The negotiating advantages of a wife increase the longer and more consistently she works. Wives who do not drop out of the labor force with the advent of children avoid the decreased power and lower marital satisfaction associated with nonworking mothers. Even intending to have a child may act as a barrier to achieving a fundamentally egalitarian marital structure by keeping couples in the modified traditional marital structure of senior-junior partners. Significant career success encouraged by an egalitarian milieu may be the key to the decision to remain childless which in turn may be essential to creating and maintaining the equal partnership in couples.

Significance to Biomedical Research and Program of the Institute: This study is relevant to the Institute's interests in the antecedents, determinants and consequences of fertility.

Proposed Course: This project expired in FY 80.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Research on Childlessness and the One-Child Family
Contract Number : N01-HD-92814
Contractor : Steiger, Fink, and Kosecoff, Inc.
Money Allocated : \$39,719 (1979); \$50,674 (1980)

Objectives: This research assessed the social-economic, psychological, and physical effects of parity (number of children born) on couples who either have completed their childbearing or are in the later years of childbearing. The social-economic variables examined are social adjustment, friends and social networks, career patterns, and income. The psychological variables are social and psychological well-being, depression, and perceived quality of life. The physical variables are current health status, resistance-susceptibility to illness, and concern about health. Couples are divided into three groups, based on the wife's age (30-39, 40-49, and 50-59), so as to obtain information about changes in the effects of parity during the life cycle. The data used are from the RAND Corporation's Health Insurance Study (HIS), which included more than 8,000 individuals (2,750 families) in four geographic areas of the United States. Some additional data needed to ascertain the voluntary or involuntary nature of fertility are to be collected by RAND. Analytical techniques include discriminant function analysis and multiple regression.

Major Findings: In research on how persons with no children, one child, two to three children, or four or more children compared in their physical and mental health lifestyle and social well-being it was found that persons with four or more children were different from those with two or three, reporting more limitations on their physical and mental health. Also, those who perceive that they have too many children appear to be more depressed, anxious and socially isolated than those who think they have too few. Neither the man nor the woman is significantly more in charge of family size. No consistent differences could be found between childless and other adults on the dimensions examined.

Significance to Biomedical Research and Program of the Institute: This research pertains directly to the Institute's interests in the consequences of fertility behavior. Childless couples and those with only children are still comparatively rare in the United States, and they tend to be negatively stereotyped as selfish, maladjusted, lonely, unhappy with marriage, etc. This research uses an excellent data source to provide objective information about childless and one-child families, including previously unavailable information about physical health.

Proposed Course: This project began in FY 79 and expired in FY 81.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : The Disruptive Effects of Fertility: A Longitudinal Study of the Sequential Consequences of Childlessness and Childbearing on the Educational and Occupational Pursuits of College-Educated Women

Contract Number : N01-HD-92816

Contractor : DePaul University

Money Allocated : \$42,098 (1979); \$6,895 (1981)

Objectives: This research studies the effects of being an only child, of having one or more children, and of being childless on such variables as educational and occupational aspirations and attainment. The goal is to develop a parsimonious model of initial aspirations, fertility and occupational choices, and relationships between these. Data are from the National Opinion Research Center's longitudinal survey of 1961 college graduates. The first wave was conducted in 1961 on a representative sample of 41,116 graduates; a subsample of 4,868 graduates completed follow-up waves in 1962, 1963, 1964, and 1968. The present research uses data from a subsample of 1,685 female graduates.

Major Findings: This study focused on the interaction between fertility intentions and career experience. While educated women in the 1960s had high fertility three years after college graduation, fertility intentions declined over the next four years. Women who postpone their desired fertility and enjoy relative success in the labor market are likely to reduce their fertility intentions.

For most educated women, childlessness is a temporary stage prior to first birth. Labor force disruption due to childbearing affects a woman's work status five years later but does not affect later career aspirations. Analysis of graduate school attainment found that disruption following childbirth had little effect on numbers of years of graduate school completed or the attainment of a graduate degree seven years after college graduation.

Significance to Biomedical Research and Program of the Institute: This research pertains directly to the Institute's interest in the consequences of fertility behavior.

Proposed Course: This project was completed in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Reciprocal Interaction Skills and Ego Identity Formation in Adolescents
Contract Number : N01-HD-92819
Contractor : The University of Texas at Austin
Money Allocated : \$79,380 (1979); \$72,122 (1980); \$9,201 (1981)

Objectives: The study analyzed data on only children and on children from two- and three-child families. Three clusters of variables believed to mediate the consequences of being an only child were examined: parental attitudes concerning family size and achievement; sibling and peer interaction; and family interaction and climate. Because only children may have different experiences than children with siblings relative to these three factors, it was expected that they would exhibit distinctive patterns of ego identity and reciprocal interaction skills. The investigators also studied the relationship of process and status to each other and their joint effects.

Major Findings: In questioning the stereotype of only children as disadvantaged, a study of white, middle-class two-parent families found that only children did not differ significantly from first and second born of two child families on adolescent developmental measures. In a second study while status variables had low predictive power, the quality of family process (as reflected in openness, validation, expression of differences and self-assertion) was related to identity development and the ability to take the perspective of others, on the part of adolescents. Results underscore the importance of the family for adolescent development which is conventionally considered dominated by peer influence.

Significance to Biomedical Research and Program of the Institute: This study is relevant to the Institute's interests in the consequences of fertility.

Proposed Course: This study expired in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Sex Role Development and the Single Child Family
Contract Number : N01-HD-92820
Contractor : Institute for Research on Social Problems
Money Allocated : \$93,285 (1979); \$96,169 (1980); \$9,903 (1981)

Objectives: The major objective of the proposed research was to study sex-role development, together with its parental antecedents, in only children. Attention was given to the consequences of being an only child for sex-role development and identity. Also, the effects of having an only child on the parents' family planning decisions and attitudes toward sex roles were considered. The research explored the strength of the parents' need for child gender diversity, the relation of this to family size decisions, and the parents' sex-role expectations in relation to family planning decisions.

Major Findings: Findings supported expectations that parents who elect to have one child would have less need for gender diversity and sex typing in their family and consequently only children would be more flexible and androgynous than those with siblings. When only children of preschool age were compared with first and second borns of two-children families, only children resembled firstborns more, while at older ages they resemble last-borns. Only children at both age levels were more flexible on some measures but the trend toward androgeny was clearer for girls, with preschool girls performing more masculine and neutral toy play than other girls.

Significance to Biomedical Research and Program of the Institute: This research is relevant to the Institute's interest in the social, psychological, and economic consequences of having one child.

Proposed Course: This project was completed in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Study of Consequences of Remaining Childless or Having Only One Child
Contract Number : N01-HD-92821
Contractor : Research Triangle Institute, Research Triangle Park, N.C.
Money Allocated : \$199,074 (1979); \$87,006 (1980)

Objectives: The investigators analyzed the 1973 National Survey of Family Growth and 1971 and 1975 Current Population Surveys and held discussions with 60 couples to assess the long-term social, economic, and psychological consequences of childlessness and of having one or two children. The research focuses on important economic, demographic, and social-psychological aspects of the quality of life: (1) marital dissolution and remarriage; (2) female labor-force participation and occupational attainment; (3) family income and standard of living; and (4) the degree of congruence between women's educational and occupational attainments and between spouses' occupational attainments. The analyses of large-scale studies of the "objective" aspects of quality of life are combined with in-depth studies of couples' experiences in these areas and in marital and parental roles, friendships, and use of financial resources and leisure time.

Major Findings: Comparisons of childless couples with those who have two or more children show that childless women are more educated, more likely to be in the labor force and to have had more continuity in labor force participation than women with children. Among white women, the childless have somewhat higher earning capacity but not higher occupational status suggesting modest career advantages of the childless. Among those separated from a first marriage, the childless and those with one child move more rapidly to divorce than those with two or more children but childless women do not remarry more rapidly or have higher probabilities of remarriage than women with moderate fertility. Entering a second or subsequent marriage seems to put pressure on couples to have a child, despite the number of previous children. The patterns of friendship and leisure of childless couples are similar to those with children, although relationships between the childless middle-aged and their parents differ.

Significance to Biomedical Research and Program of the Institute: This research is related to the definition and consequences of fertility and fertility decisions.

Proposed Course: This project expired in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Societal Consequences of Adolescent Childbearing
Contract Number : N01-HD-92822
Contractor : The Urban Institute
Money Allocated : \$117,398 (1979); \$199,579 (1980); \$208,122 (1981)

Objectives: The proposed research will provide information at the national level on public expenditures to teenage parents through various programs: AFDC, Medicaid, Food Stamps, etc. Three types of estimates will be calculated. First, there will be calculation of actual expenditures for a given year (1975) on births to teenagers and nonteenagers. Next, the 1975 data will be projected forward to 1990 using a number of different assumptions (seven in all). These assumptions relate to different probabilities of birth among teenagers and other, different assumptions about illegitimate pregnancy, and school dropout rates among teenagers if they get pregnant. The third estimate will cumulate over the period 1975 to 1990 the cost to the government per mother for teenage versus non-teenage mothers who bore their first child in 1975. This group of teenage mothers will be treated as a cohort and the cost of their cumulative fertility to the government will be examined.

Major Findings: Marriage and school enrollment both reduce labor force participation among teenage females. Among whites, the presence of a child six or younger reduces the likelihood of employment; but no similar effect is found for nonwhites. The negative effect of marriage on employment is also stronger among whites than nonwhites. Among those active in the labor force, the hours worked were estimated. Marriage and school attendance were found to depress the number of hours worked, though in this case the negative impact of marriage on school attendance is greater for nonwhites than for whites. The presence of a child six or younger was found to be associated with working more hours among nonwhites and fewer hours among whites. Race, marital status, and the presence of a young child were not associated with wage rates among employed teenagers.

Significance to Biomedical Research and Program of the Institute: The project offers an ideal opportunity to assess the public sector costs of adolescent childbearing, a topic of considerable interest to the Institute.

Proposed Course: This project is scheduled for completion in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Estimating and Forecasting Money Expenditures on Children
Contract Number : N01-HD-92823
Contractor : Mathtech, Inc.
Money Allocated : \$94,802 (1979); \$43,752 (1981)

Objectives: This project will analyze the cost of children based on the economic theory of indirect utility as embodied in a transcendental log functional form. The investigators are using the 1972-1973 consumer expenditure survey as the basis for estimating the cost of children, and combining these cost estimates with a separate analysis of life cycle income to predict cost of children from the year 1980 through 2000.

Building on consumer demand theory, demand functions are to be estimated in which consumption is a function of prices and income. The resulting demand functions are substituted back into the utility function, producing an indirect utility function. The transcendental logarithmic indirect utility function is adopted as the functional form. This combined with Roy's identity permits derivation of the implied consumer demand functions for each commodity. Lifetime income profiles for head and spouse are being developed and used in the total expenditures equation to forecast expenditure category. The marginal cost of an additional child is then to be computed using several standard of living measures and a "relative expenditures" approach.

Major Findings: The first child from birth to age five costs the family about 20 percent additional expenditures to attain the standard of living of a childless family. As the single child ages, cost seems to decline somewhat, with the exception of expenditures on education. The same pattern appears to hold for households with several children. The cost of the last child does not appear to be lower than the cost of the preceding children while the cost of children increases in absolute terms.

Significance to Biomedical Research and Program of the Institute: This research pertains directly to the Institute's interest in the consequences of fertility.

Proposed Course: This project was completed in FY 81.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Estimating the Cost of Children in the United States
Contract Number : N01-HD-92824
Contractor : Carolina Population Center, University of North Carolina
Money Allocated : \$119,553 (1979); \$81,213 (1980); \$65,395 (1981)

Objectives: Three different methodological approaches will be used to estimate the direct, out-of-pocket costs of rearing children to an age of financial independence. Each method will utilize the 1972-1973 Consumer Expenditure Survey data for preparing basic estimates, supplemented in some instances with other data, such as the 1976 Health Interview Survey. The first method will estimate child costs in terms of additional family income required to maintain a given standard of living as children are born and mature ("a standard of living" approach). The second method constructs unit consumer scales and estimates child cost in terms of unit proportions for each category of expenditure (an extension of the "unit consumer scale" approach). The third method makes use of recent developments in demand system analysis that incorporate demographic variables directly into household demand equations (a "utility-based" approach). In addition, 1972-1973 data will be compared to 1962 data for examination of trends and change.

Major Findings: Preliminary results show that the cost of children is a sizable component of the average American family's expenditure stream. A boy, born to a father age 25, will (in 1981 prices) be responsible for family expenditures of approximately \$62,500 during the first eighteen years of life. Expenditures on girls appear to be approximately the same. However, there are some marked differences in the commodity distribution of expenditures on girls and boys. For example, 25 percent of total expenditure on a boy is for food while only 22 percent of total expenditure on girls is for food. Transportation accounts for 18.3 percent of the total for boys and 17.2 percent for girls, while clothing and clothing maintenance account for 11.7 percent for girls and only 9.5 percent for boys.

Examining the level of expenditures by age of child, subdivided into six groups, it was found that senior high school students account for approximately 30 percent of total expenditures, junior high students 19.5 percent, and infants from birth to age three, 15 percent. The middle years from age three to 13 are the lowest cost age periods. In an analysis of "scale effects" it was discovered that family size, per se, has marked effects on family expenditure independent of individual specific requirements and family income. Marked differences between single-person and multi-person households have emerged. For multi-person households the effect of family size varies with commodity: scale economies for shelter, clothing, household equipment and operations, and fuel and utilities; scale diseconomies for recreation and transportation.

Significance to Biomedical Research and Program of the Institute: This research pertains directly to the Institute's interest in the consequences of fertility.

Proposed Course: This project is scheduled for completion in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Research on the Economic Determinants of Fertility
Contract Number : N01-HD-92825
Contractor : Data Resources, Inc.
Money Allocated : \$84,371 (1979); \$67,117 (1980)

Objectives: Cross-sectional estimates of the costs of maintaining a child through its dependent years have been calculated using data derived from the 1972-1973 Consumer Expenditure Survey Summary and Detailed Interview tapes. Estimates of child costs have been made by selected family characteristics including family size, family income, age of parents, residential area, occupation and education of family head. Separate estimates of expenditures have been made by broad categories of consumer goods and services such as food, housing, medical care, and education. The allocation of expenditures by category among family members have been made using a modification of a method developed by Edward Lazear of the University of Chicago and Robert Michael. The cross-sectional estimates have been used as the basis for forecasting year-by-year expenditures for a child born in 1980 through its period of dependency. The forecast method utilizes an age-income model developed by Data Resources, Inc. which is linked to the agency's macroeconomic model of the U.S. economy. Separate forecasts are being developed for families of different characteristics, including three levels of income. Forecasts of summated costs will be expressed in discounted and undiscounted form under three different assumptions of inflation trends.

Major Findings: The research showed that expenditures on children are substantial: about 24 percent of undiscounted real family income from birth to age 22 for a male child born to an average family (assuming four years at a residential private college). Netting out the child's earnings, this percent falls to about 22 percent. Expenditures on food comprise the largest percentage of the total, followed by housing, education, transportation, health care, and clothing. Expenditures are relatively high in the birth year after which they decline to age five and then rise continuously. Expenditures rise with the number of children and with family income, although in both cases by a less than proportionate amount. Girls are found to be more expensive than boys. Expenditures were also elevated for urban children and (income held constant) for children born to young and/or Black parents and for children raised in the South. Real expenditures on children will be higher if the economy grows unexpectedly briskly and inflation falls off rapidly, but these higher expenditures will be a smaller fraction of real family income.

Significance to Biomedical Research and Program of the Institute: This research pertains directly to the Institute's interest in the consequences of fertility.

Proposed Course: This project was completed in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : The Consequences of Being and Having an Only Child on Intelligence, Interpersonal Orientation, Attitudes and Time Use
Contract Number : N01-HD-92830
Contractor : The University of Texas at Austin
Money Allocated : \$134,575 (1979); \$76,941 (1980); \$12,797 (1981)

Objectives: This research comprises a series of three interrelated studies to assess the consequences of being and having an only child on intelligence, interpersonal orientation, attitudes, and time use, over a two-year period. The research is designed to examine the consequences of growing up without siblings particularly (but not solely) on the development of interpersonal skills and IQ. The research studies are grounded on the confluence model of intellectual development proposed by Zajonc and Markus, which accounts for the relationship between family size and intelligence by explaining the IQ discontinuity of only children as caused by the fact that only children do not have younger siblings to tutor.

Major Findings: In testing hypotheses from the confluence model that only children are disadvantaged in IQ by not having younger siblings to tutor, negative findings failed to support the hypothesis. Only children and last-borns of two-child families scored no lower on intellectual ability than firstborns of two-child families. There was no support for the hypothesis that tutoring a younger child results in gains in intellectual capacity for the tutor. Only children were not rated as possessing less desirable personality characteristics than children with siblings. Only children were not less effective tutors than firstborns, only children do not demonstrate lowered sociability, one-child parents are no less sociable than parents of two or three children. Parents of only children spent no less time in child-oriented activities than other parents. In general, the research suggests that being or having an only child has little negative impact.

Significance to Biomedical Research and Program of the Institute: This study is relevant to the Institute's interest in the antecedents, determinants, and consequences of fertility.

Proposed Course: This study was completed in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Contraceptive Decision Making in Adolescent Couples
Contract Number : N01-HD-92835
Contractor : American Institutes for Research in the Behavioral Sciences
Money Allocated : \$54,510 (1979); \$43,228 (1980)

Objectives: This study investigates couple communication and decision making regarding contraception among young unmarried sexual partners. Factors which influence these interactions in teenagers and the nature of the effects of such communication on fertility decision making and actual contraceptive practice have been examined. The goal was to provide a sufficient level of understanding of processes underlying communication and decision making in teenage couples, as they relate to contraception, to permit the development of a theory and model for these phenomena. Data for the study were collected by means of in-depth interviews with 83 couples, with the requirement that the female partner be between 15 and 18. Included were information on demographic factors, situational variables related to contraceptive knowledge and use, social interactions, and psychological variables.

Major Findings: In examining communication and decision making regarding contraception among young unmarried couples it was found that the couples who were best protected were ones in which one partner took charge of contraception, rather than having the responsibility shared. On the other hand, couples whose overall communication was high tended to be effective contraceptors, suggesting that individuals determined to avoid a pregnancy may use communication more as a negotiating device to persuade partners than as a problem solving device, to jointly select contraceptive methods.

Significance to Biomedical Research and Program of the Institute: This project pertains directly to the Institute's interest in contraceptive behavior.

Proposed Course: This project expired in FY 81.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Collection of Data in Cycle III of the National Survey of Family Growth Concerning Unwanted Childbearing and Contraceptive Practice in the Later Reproductive Years
Contract Number : 1-Y01-HD-01045-00
Contractor : National Center for Health Statistics
Money Allocated : \$204,130 (1980); \$358,932 (1981)

Objectives: This project involves data collection and tape preparation for that portion of National Survey of Family Growth Cycle III (NSFG III) relating to contraceptive practices and unwanted childbearing among women 30-44. NCHS will deliver a complete documented data tape for the 1981 survey, i.e., all data for all women interviewed ranging in age from 15-44. The NSFG III is the latest in a succession of national fertility surveys that began in 1955. These surveys are the source of data about contraceptive practices, wantedness of births, sterilization, and correlates of these behaviors for the U.S. as a whole. The questionnaire deals specifically with knowledge of birth control and reproductive processes; detailed pregnancy history; history of use of contraceptives and wantedness and planning status of births; sterility and subfecundity; use of family planning and infertility services; and demographic characteristics, e.g., socioeconomic indicators, marital history, child care, race, and ethnicity. The structure of this survey is such that meaningful comparisons can be made with earlier time periods, and the oversampling of Black women ensures comparisons between Blacks and whites.

Significance to Biomedical Research and Program of the Institute: This project will provide valuable data about the contraceptive practices and fertility behavior of women in the U.S. These data will be useful to a wide range of biomedical and behavioral scientists.

Proposed Course: This two-year interagency agreement was begun in FY 80, and is scheduled for completion in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Contraceptive Decisions: Spousal Relationship, Method
Commitment
Contract Number : N01-HD-02802
Contractor : Center for Consumer Research, University of Florida
Money Allocated : \$72,639 (1980); \$64,414 (1981)

Objectives: A longitudinal investigation of couple decision making and choice behavior among contraceptive alternatives was conducted with 360 randomly identified couples in the Gainesville, Florida area. The investigation pays particular attention to the application of the expectancy value model and is concerned with the nature of the husband and wife input to decisions, concerns for life cycle differences, demographic characteristics, and clusterings based on the nature of the relationship evinced by the couple.

Major Findings: Most attitudinal support is generated for male sterilization procedures followed by female sterilization procedures, condom, pill, diaphragm, IUD and foam in that order. Husbands and wives disagreed on attitudinal support for the pill and for the condom. Age of couple and the nature of the relationship accounted for differences.

Research suggests that the most important characteristics of choices among contraceptives are: (1) being sure of avoiding pregnancy; (2) using a birth control method that lets husband and wife control when they have children; (3) avoiding major health problems that result from using a birth control method; (4) using a birth control method that is easy to use; (5) avoiding having the birth control method affect the wife's everyday mood; and (6) avoiding birth defects.

Significance to Biomedical Research and Program of the Institute: This research pertains directly to the Institute's interest in the antecedents and determinants of fertility.

Proposed Course: The research will continue into FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Interdisciplinary Assessment of Fertility Management in a High Fertility Community
Contract Number : N01-HD-02803
Contractor : Department of Community Medicine, University of Kentucky
Money Allocated : \$129,301 (1980); \$154,456 (1981); \$104,468 (1982)

Objectives: This interdisciplinary three-year project aims at describing fertility regulating attitudes, perceptions and practices, as well as the factors associated with these variables, in a high fertility Eastern Kentucky Appalachian county of about 13,000 people. Three strategies will be employed. First, a community inventory will be undertaken to determine general access to fertility regulation information, supplies, and services, and to assess the views of community leaders and the general community atmosphere regarding family planning. This will involve structured and unstructured interviews and a traditional ethnographic approach. The second strategy includes interviews with married females, and 100 of their husbands, covering knowledge and attitudes regarding family planning, fertility history, family conjugal roles, value and personality factors, and sociodemographic variables. The third strategy entails in-depth interviews, based on factors which emerged using the other two strategies, with 100 women and their husbands. Analyses of the data will be both descriptive and exploratory.

Major Findings: In the county under study family planning services and birth control methods are readily available; general knowledge of birth control methods and family planning services are practically universal. Most of the study population approve of using birth control to limit family size, and most couples have fairly definite ideas concerning the number of children desired, practicing family planning to achieve the desired number. There appears to be a growing popularity of sterilization as a permanent method of birth control for married couples in the community.

Significance to Biomedical Research and Program of the Institute: This research should provide insights into the dynamics of fertility regulation that are unobtainable by single disciplinary approaches. The results are likely to increase understanding of the complex of variables that affect birth planning at the community, family, and individual levels.

Proposed Course: This project is scheduled for completion in FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Consequences of Childlessness for Older Men
Contract Number : N01-HD-02804
Contractor : The University of California at Los Angeles
Money Allocated : \$56,387 (1980); \$17,646 (1981)

Objectives: This is a study of the psychological, social, and emotional consequences of childlessness among married men 60 years of age and over. It is hypothesized that the relation between parity (childless or parenthood) and well-being is moderated by social-psychological variables such as social contact and congruence between fertility desires and outcomes. One hundred and fifty men over age 60 with children are compared with 150 childless older men on a variety of variables including several measures of well-being, congruence between desired and actual family size, satisfaction with family size, expectations of parity outcomes, social interaction, and sociodemographic variables.

Major Findings: In examining if childlessness has negative effects on the social-psychological well-being of older married men and their wives, hypotheses tested showed that fathers and childless men have similar levels of well-being. Among childless men, voluntariness of status had no effects on well-being. The number of children had no effect on fathers' well-being or fathers' satisfaction with children. Men with all sons had significantly lower well-being, higher depression and higher lonely/dissatisfaction scores than did men with all daughters, and somewhat greater depression than did men with children of both sexes. Protestants had higher well-being than Catholics or Jews; the latter showed similar scores in well-being. The more satisfying a father's social interaction with persons other than children, the more satisfied he is with contact with children, controlling for amount of child contact.

Significance to Biomedical Research and Program of the Institute: This study is relevant to the Institute's interest in the consequences of fertility.

Proposed Course: This study was completed in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Research on the Societal Consequences of Adolescent Child-bearing Public Assistance Costs, 1975 and 1977
Contract Number : N01-HD-02837
Contractor : JWK International Organization
Money Allocated : \$90,845 (1979); \$33,506 (1980)

Objectives: This project uses the 1975 and 1977 AFDC Recipient Characteristics Surveys for an analysis of the costs of teenage childbearing among the population receiving public assistance. The direct dollar costs of being a prior teenage mother are being obtained for AFDC recipients aged 20 and 30 for AFDC payments, food stamps, other state and local assistance payments, and emergency payments. The indirect impact of teenage motherhood on these same costs will also be explored. For AFDC mothers currently in their teens, total direct costs will also be cumulated and indirect costs will be explored. In addition, reliance upon Social Services will also be tabulated. Finally, development of a causal model is proposed to examine the number of months mothers have received AFDC payments.

Major Findings: This study demonstrates that long-term cost consequences can be systematically traced through the complicated life events generated by an early age at first birth. Modified versions of the same causal model are used to investigate the cost of Food Stamp payments within AFDC households and the duration of AFDC payments. A mother's age at first birth has only a weak direct influence on whether or not an AFDC family receives Food Stamps, which depends primarily on the overall composition of the household. Mother's age at first birth exerts a negative indirect effect on the amount of the Food Stamp bonus, primarily through the larger number of children. The net indirect effect of a one year increase in welfare mother's age at first birth generates an expected savings of about \$56 million in Food Stamp costs. Mother's age at first birth is found to have a direct effect on the duration of AFDC payments, but few indirect effects, with a total impact of about 2.7 months shorter current duration for each year's postponement in the age of first birth. The AFDC cost savings from shorter duration are estimated as \$873 million, in 1975, from a one year increase in age at first birth.

Significance to Biomedical Research and Program of the Institute: This project addresses an important consequence of adolescent fertility. It has high policy relevance for HHS programs.

Proposed Course: This project was completed in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Research on the Societal Consequences of Adolescent Child-bearing
Contract Number : N01-HD-02838
Contractor : Bokonon Systems, Inc.
Money Allocated : \$109,046 (1980)

Objectives: This study focuses on the public sector costs and consequences of adolescent childbearing at the local level. The existing data set permits the investigators to differentiate between welfare costs due to adolescent childbearing and those due to other services a woman might receive. The data allows for comparison of costs for teenage mothers with costs for older mothers also receiving services. The level of detail in the data allows the differentiation between medical, social service, and food costs.

Major Findings: In a comparison of welfare costs for women whose first birth was as a teenager (TAP's) with those who delayed conception until their post-teen years (N-TAP's), it was found that while TAP's outnumber N-TAP's in the under 30 age group, N-TAP's predominate in the over 30 age group. It is suggested that after 30, TAP women tend to leave the welfare rolls, while N-TAP mothers increase dramatically. Each group has unique problems in that women who enter early (TAP's) have grown children while still young enough to consider other career opportunities, while N-TAP's enter later with younger children forcing them to stay on welfare longer.

Significance to Biomedical Research and Program of the Institute: The project offers an opportunity to assess the public sector costs of adolescent childbearing, a topic of considerable interest to the Institute with both social and biomedical implications.

Proposed Course: This project was completed in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Longitudinal Analysis of Family and Household Structure
Contract Number : N01-HD-02849
Contractor : The Urban Institute
Money Allocated : \$787,000 (1981)

Objectives: This research consists of three studies of the structure and the behavioral patterns of families and households. The first study will describe the sequence and spacing of marital and childbearing events of women over their lifetimes. The second study will examine changes in marital status composition, applying techniques of multiregional population analysis to data on flows of individuals among marital status categories throughout their lifetimes. The final study will describe the frequency of family structures and living arrangements of children, and will estimate the probability of moving from one family type to another.

Major Findings: There has been an upward trend in the median age at marriage for white women born since 1940. The median age of first marriage for white women born in 1940-44 was about 20.5, while for women born 1955-59 it was about 21.9. If these trends continue, the median age of first marriage for white women born 1975-79 may be as high as 24.2. For Black women, the median age of marriage is much higher and rising more rapidly. The effects of business cycles upon age of marriage for white women is to delay marriage during economic downturns, while the marriage pattern of Blacks does not appear to respond to business cycles.

A rising trend in percentages of marriage likely to end in divorce is evident based on 1970s data. The probabilities of having a marriage end in divorce are 30 percent for women and 25 percent for men. The risk of marriage ending with death of spouse is 47 percent for women and 18 percent for men. While remarriage rates are high (74 percent for women and 83 percent for men) the average duration of divorce for women is 13 years while that of men is 5.8 years. Percentages of children who are expected to live with only one parent at some time before age 18 are increasing for recent birth cohorts.

Significance to Biomedical Research and Program of the Institute: The proposed analyses will be useful not only for describing the micro-level processes that occur in the lives of individuals, but also for making projections of the future distribution of the population by family type.

Proposed Course: This contract is scheduled to run through FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Changing Patterns of Marriage and Divorce in the United States
Contract Number : N01-HD-02850
Contractor : University of Michigan
Money Allocated : \$199,800 (1980)

Objectives: The purpose is to analyze first marriage probabilities for Americans born since 1880 to determine the patterns of change in terms of short-term fluctuations and longer-term trends.

Major Findings: The short-term fluctuations include heightened probabilities of marriage in the years just before and just after the two world wars, surrounding lowered probabilities during American involvement in those wars; and lowered probabilities during the Depression years of the early 1930s. Longer-term trends vary somewhat for different parts of the population. In particular, there seems to have been very little change among those over the age of 28. Among whites in their 20s, there was a gradual increase in probabilities of marriage during the forty or so years preceding World War II, followed by much higher rates after the war--the "marriage boom." Since 1970, however, probabilities have dropped precipitously, and the age pattern of first marriage probabilities by age in 1979 was remarkably similar to that observed in the period before the first World War. For Blacks, the marriage probabilities at each age level have declined relative to those for whites. In particular, Blacks were considerably more likely than whites to marry before the age of 20 in the first part of this century; in the 1950s, marriage probabilities for Black teenagers began to fall, and in the 1970s they dropped below the probabilities for white teenagers.

Significance to Biomedical Research and Program of the Institute: Changes in age of marriage and probabilities of marriage have important effects on marital fertility levels relating to the issue of the determinants of fertility and population growth in general.

Proposed Course: This project is scheduled to be completed in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Demographic Perspectives on the Consequences for Children of Changing Marital Patterns
Contract Number : N01-HD-02852
Contractor : University of Wisconsin at Madison
Money Allocated : \$215,117 (1980)

Objectives: The proposed research will use data from the 1976 National Survey of Family Growth and from the 1975 and 1980 (June) Current Population Surveys to conduct five specific analyses: 1) life-table analysis of children's experience of marital disruption, estimating the cumulative experience of being in a single-parent family by time since disruption and cumulative proportions of children experiencing disruption by age; 2) a study of trends in children's experience with marital disruption; 3) a cross-tabulation of data to describe the household living arrangements of children who have experienced marital disruption, in terms of number and types of parents/stepparents and siblings; 4) and analysis of intermarital fertility including analysis of contraceptive use and family planning status prior to the birth; 5) a life-table analysis of the occurrence and timing of second-marriage births.

Major Findings: A recent doubling in children's experiences of second marital disruptions is suggested. One-sixth of all children have step or half siblings, and about one quarter are not living with both of their natural parents. For children of remarried mothers, these proportions are three-fifths with partial siblings and two-thirds not with both parents.

The June 1980 CPS data suggest that earlier estimates of children's experience with marital disruption were overestimated due to age of mother constraints. The cumulative experience implied by rates in the 1970s may be about a quarter of all children, but age-specific rates have increased over the 1970s, so recent rates may imply higher levels than previously noted.

Little change was found in contraception for the month when separation occurs. Separation increases nonuse of contraception pointing to births between marriages as due to continuation of pre-separation patterns resulting in accidental pregnancies that would have occurred within marriage.

Significance to Biomedical Research and Program of the Institute: A major strength of this research lies in its use of recently collected data to determine current patterns of marital disruption and the subsequent formation of new households.

Proposed Course: This project is expected to continue through FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Changing Patterns of Household Structure: A Cohort Analysis
Contract Number : N01-HD-02853
Contractor : University of North Carolina
Money Allocated : \$21,810 (1981)

Objectives: The research proposes to graphically depict changing patterns of household structure for different cohorts by sex, urban-rural residence, and race. In addition to national results, information for 10-18 states, representing various regions, will be presented separately. Data from the 1940, 1950, 1960, and 1970 censuses will be used. Major goals are to show the percent of each cohort 1) whose relationship to head of household is child by age, 2) classed as head of household by age, 3) classified as grandchild of head of household by age, 4) classified as parent of head of household by age, and 5) classified as other relative by age. In addition, the research is to calculate the ratio of unmarried females ages 35-59 to persons 65 and over for whites and nonwhites in different regions for the period 1900 to 1980, to assess the extent of changes in the availability of such women for the care of elderly family members.

Major Findings: Research found an increase in proportion classed as child between the ages of 0-4 and 10-14, due to the decline in proportion classed as grandchild at these ages. The decline of the proportions of elderly living with their children is well documented in this project.

The study also documents the virtual disappearance of unmarried females over the age of 30 available for the care of the elderly. As a result of increased marriage rates and increased longevity, resulting in more people over 65, the ratio of single females per 100 individuals over 65 has declined from 28 per 100 to nine per 100. Among nonwhites the decline has been less dramatic--from a ratio of 21 to 100 in 1900 to 14 to 100 in 1970. Among nonwhites the single females were never as large a resource for the elderly due to the higher labor force participation of nonwhite females.

Significance to Biomedical Research and Program of the Institute: The project is expected to extend appreciably the empirical knowledge on past trends and current patterns of marriage, divorce, and household formation.

Proposed Course: The project expired in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Reproductive Behavior and Fertility Regulation Among 20-29
Year Old Unmarried Women
Contract Number : N01-HD-02857
Contractor : Temple University
Money Allocated : \$43,644 (1980)

Objectives: This project examines a national random sample of 1000 unmarried women, aged 20-29, to study factors associated with their sexual and reproductive behavior and contraceptive practices. Special attention will be focused on (a) circumstances surrounding onset and level of sexual activity, (b) appreciation of and attitudes toward risks of pregnancy, (c) contraceptive practices, (d) factors influencing contraceptive effectiveness, (e) relation of abortion attitudes and psychological and economic consequences of premarital pregnancy.

Significance to Biomedical Research and Program of the Institute: The results of this research should contribute to knowledge on an unstudied segment of the population on the topics of reproduction and contraception which are of major concern to the Institute.

Proposed Course: This project was converted to a grant in FY 82 and is expected to be completed in FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : National Longitudinal Survey--Adolescent Fertility and Family Formation
Contract Number : Y01-HD-11048-00
Contractor : Department of Labor
Money Allocated : \$50,000 (1981); \$499,958 (1982)

Objectives: The purpose of this project is to augment the fourth wave of the National Longitudinal Surveys of Youth with questions needed for the analysis of fertility behavior. The Youth Surveys consist of six annual interviews over a five-year period with a national sample including overrepresentation of Blacks, Hispanics and poor whites. The questions to be added include pregnancy histories, information on child care arrangements for children under five, marital expectations and shift work experience of the spouse. Together with the information on other topics, the impact of employment, fertility and child care patterns on family life will be assessed.

Significance to Biomedical Research and Program of the Institute: The data collected are likely to become the major source of research material on the causes and consequences of early family formation in the early 1980s.

Proposed Course: This project is scheduled for completion in FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Support of Bibliographic Preparation of Population Index
Contract Number : N01-HD-12138
Contractor : Princeton University
Money Allocated : \$98,288 (1971); \$72,984 (1973); \$90,879 (1974); \$99,333
(1975); \$94,235 (1976); \$93,089 (1976 TQ); \$99,821 (1977);
\$110,193 (1978); \$116,123 (1979); \$122,412 (1980); \$30,603
(1981); \$240,432 (1982)

Objectives: The purpose of this project is to support the bibliographic preparation by Office of Population Research staff of Population Index as a quarterly journal containing bibliographic information and special articles in the population field. Printing and distribution costs are paid by other sources of funding.

Major Findings: In 1981 Population Index published four quarterly issues and the annual cumulative index, as well as continuing the computerization of production and the establishment of an information retrieval data base. The process of data entry of the index citation is current with journal production. Abstracts and thesaurus terms have been included with the 1981 citations. In March 1982 portions of Population Index data base became available through POPLINE at the National Library of Medicine, and citations are added on a monthly basis. The style of bibliographic citations is being adapted to facilitate the production of the journal from the tapes prepared for POPLINE. Princeton, Johns Hopkins, and Columbia Universities jointly produced the Thesaurus (published in 1981) as a guide for the incorporation of demographic, sociological and economic information as well as family planning and biomedical information. A supplement to the Population Index bibliography covering the years 1969-1981 is scheduled for publication in 1982. Items published in the past year include an estimation of the completeness of registration in a closed population and adjustment of U.S. State and local area census counts.

Significance to Biomedical Research and Program of the Institute: Used throughout the world, Population Index is indispensable to demographic research and teaching, family planning, and to approaches to economic and social development. References to health research, planning, and delivery systems make it essential to the health mission of NIH in the population sciences.

Proposed Course: This contract has been extended into FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Demographic Analysis of Family and Household Structure
Contract Number : N01-HD-12802
Contractor : The Johns Hopkins University
Money Allocated : \$136,684 (1981)

Objectives: Data from the Public Use Tape from the June 1980 Fertility and Marriage History Supplement to the CPS will be used to deal with two major topics: 1) the extension of families over more than one household due to links formed by children from previous marriages; 2) current and projected rates of marriage, dissolution, and remarriage. Separate analyses will be made for different subgroups, by age, sex, race, and education.

Major Findings: Preliminary findings from this research show that the recent fall in annual remarriage rates reflects a delay in remarrying in recent divorce cohorts (due in part to an increase in cohabitation prior to remarriage) rather than a drop in the lifetime probability of remarriage. Although the western European trends may reflect a reduction in the probability of remarriage, United States trends after divorce indicate that marriage is still a central aspect of family life and divorced Americans today are not less likely to remarry than in the 1960s, although they are taking a few months longer, on average, to do so.

Significance to Biomedical Research and Program of the Institute: This project is expected to extend appreciably the empirical knowledge on current patterns of marriage, divorce, and household formation.

Proposed course: This project is scheduled for completion in FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Household and Family Demography of Hispanics, Blacks and
Anglos
Contract Number : N01-HD-12812
Contractor : University of Texas
Money Allocated : \$120,860 (1981); \$113,123 (1982)

Objectives: The research will focus upon patterns of household and family structure among Mexican-Americans, Puerto Ricans, Cubans, Blacks, and non-Hispanic whites. This study will be founded upon a taxonomy based on a household composition dimension defined by size, age, and sex, and a family dimension defined by biological, marital, and non-familial relations. Estimates of the distribution of the relevant subpopulations across household-family statuses will be developed for 1960, 1970, and 1980, and compared over time and across groups. Socioeconomic correlates of household family types will be assessed.

The conviction underlying the study is that a detailed classification of household and family structure is a necessary prerequisite for understanding intergroup differences. The goals of the work are to (1) develop a cross-classification system combining 28 household characteristics, (2) use that system to compare the family and household structures of the different ethnic groups, (3) examine how selected household-family types differ across race/ethnic categories by relevant socioeconomic correlates, and (4) analyze group changes in household-family structure over the 1960-80 interval.

Major Findings: In studying household family type, contrasting patterns emerged. The probability of Mexican American females living alone is quite low along with the prevalence of large Mexican households. Puerto Ricans are characterized by higher-than-expected levels of multi-adult households and exceed all other Hispanic populations in the very high ratios of unmarried women with children. While in 1960 the Cuban population had the single male category as its highest probability, by 1970 the highest probabilities were for never-disrupted or remarried couples with children and parent(s) of the couple present in the household. Non-Hispanic Blacks show overrepresentation of marital disruption and single female-headed households with two or more children. With the exception of Cubans, all groups followed societal trends in decline of mean family size and increased single person households. For Cubans the trend was reversed with a decline in proportion of households with never-married head.

Significance to Biomedical Research and Program of the Institute: This project will provide basic information regarding the changing nature of the distribution of very important subgroups of the U.S. population across family and household statuses, providing the basis for through-time and cross-group comparisons.

Proposed Course: This research will continue through FY 84.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Patterns of Household Structure of the Elderly: Determinants and Future Trends
Contract Number : N01-HD-12813
Contractor : The Urban Institute
Money Allocated : \$72,054 (1981)

Objectives: This study of the interactions between family and household composition has six major objectives. The first is to estimate the probabilities that an old individual or couple lives in each of a set of possible household types, given the availability of specific categories of biological relatives. The second is to assess the effect of specific economic, sociological, and demographic determinants on household structure for the elderly, taking account of variations across individuals in the number and characteristics of available kin. The third is to assess the impact of attributes of available kin on observed household patterns. The fourth is to assess the dynamics of household composition as it responds to changes in age, marital status, health status, and employment status. The fifth is to develop projections of available kin for the aged through the year 2015. The sixth is to assess the implications for future household structures among the aged of a variety of factors mentioned above. This project covers a two-phase program of research. In the first part of the project, micro-level data will be utilized from the LRHS (Longitudinal Retirement History Survey) conducted by the Social Security Administration. Four data points are available for 1969, 1971, 1973, and 1975. The data focus on the elderly, and the data set provides the opportunity to link together households and family data. The survey includes information not only related to current household arrangements for certain elderly groups--defined here as specifically those aged 65 to 69--but also provides data on living kin. Thus, the basic purpose of the proposal is to demonstrate the effect of surviving kin networks on household arrangements for the elderly aged 65 to 69, and apparently the data will make it possible to make estimates for the white and the nonwhite households.

Major Findings: It was found that Black women are more likely, relative to whites, to live with either their children or with others than to live alone. Home ownership reduced the probability of living with children, rather than living alone, among formerly married women. However, home ownership did not affect the probability of living with either parents or others, relative to the probability of living alone. In contrast, home ownership among never-married women greatly increased the probability of living with their parents, relative to the probability of living alone. Finally, income tended to reduce the likelihood of living with nuclear family relatives, but did not affect the likelihood of living with others.

Significance to Biomedical Research and Program of the Institute: This research is expected to make more clear the relationship between the nature of the family network of the elderly and the distribution of the elderly across household structures.

Proposed Course: This project will be completed in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Changing Living Arrangements and Family Formation of Young Adults
Contract Number : N01-HD-12814
Contractor : The Rand Corporation
Money Allocated : \$96,950 (1981); \$113,774 (1982)

Objectives: This research focuses on the relationship between experience in nonfamily living and family formation, family building, and dissolution. The proposition that experience in nonfamily living during young adulthood affects the timing and nature of subsequent family formation will be tested. Three questions will be addressed: (1) Are young adults who have lived in nonfamily households more likely than others to postpone or even forego marriage? (2) Does the experience of nonfamily living before marriage affect the likelihood and timing of a first birth, attitudes toward family size, number of children expected, and number of children born? (3) Does the experience of premarital nonfamily living affect the stability of subsequent marriages? The role of nonfamily living in the transition from single to married, from childless to parent, and from marriage to dissolution will be examined as well as the effect of nonfamily living on the timing of first marriage, the timing and tempo of fertility, and the chances of marital dissolution. The analysis will utilize three longitudinal data sets: (1) the Parnes Young Men and Young Women Surveys, (2) the Panel Study of Income Dynamics, and (3) the National Longitudinal Study of the High School Class of 1972.

Significance to Biomedical Research and Program of the Institute: This study will contribute greatly to our knowledge of the effects of nonfamily living, a phenomenon of increasing importance in the U.S.

Proposed Course: This research is expected to continue through FY 84.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Changes in the Structure of Central Appalachian Mountain Families and Households, 1900 to 1976
Contract Number : N01-HD-12815
Contractor : University of Kentucky
Money Allocated : \$70,352 (1981)

Objectives: This project will compare household and family structure in the Central Appalachian Region at three points in time: 1900, 1958, and 1976. Three sources provide comparable data on household and family composition at these points: individual household schedules from the Census of 1900, the 1958 Appalachian Studies household survey, and the 1976 Survey of Income and Education (SIE) done by the Census. It is planned to put the data from the two earlier studies into the same format as the SIE data. There are 420 households for the 1958 point, and a sample of 550 will be selected for 1900.

Changes in the relationship of household to family structure at the three time periods will be analyzed. Observed structural modifications will be related to known social and economic changes, though this will not be a statistical procedure. Changes in household member characteristics such as age, marital status, labor force status, education, and occupation will be analyzed by household status.

Major Findings: Results to date refer to the year 1958 which was one of severe economic crisis in the Central Appalachian region. Heavy out-migration, a deficit of young adults, a decline in the number of young children and high proportions of middle-aged adults characterize the structure of households and families. The average age of household heads was nearly 50 years, and less than a fifth were under 30. Despite the out-migration and lower birth rate, average household size continued to exceed the national average because single person households remained rare in the mountains. Nearly all households were composed of primary families headed by a male, who was likely to be working as an operative. Only about a fifth of the wives were in the labor force. The educational level of household heads was low and less than 20 percent of the households reported incomes in excess of \$6,000.

Significance to Biomedical Research and Program of the Institute: This study provides a unique opportunity to study the traditional American household/family that is frequently referred to as a desired model for American society today.

Proposed Course: This project is expected to be completed in FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Effects of Family Size: A Critical Review of Research
Since 1973
Contract Number : N01-HD-12816
Contractor : American Institutes for Research
Money Allocated : \$82,716 (1981)

Objectives: This research focuses on the literature since 1973, but will integrate the entire body of knowledge relating to the effects of family size. Theoretical implications will also be analyzed, and directions for future research will be recommended. Among other aims, this project will go beyond similar types of reviews in the following respects: (1) "family size" will be broadened to include childless couples, single-parent families, and other family structures (e.g., widowed and divorced); (2) measurement problems in definitions of family size will be examined (e.g., taking step-relatives into account); (3) trends in the effects of family size will be extended to include a wider range of family size effects than has typically been the case in previous work. In addition, this review incorporates an awareness of various methodological concerns (e.g., questions of causality, confounding variables, and measurement problems). Thus a very wide source of data will be tapped, and with attention to a number of outcome variables (e.g., household structure and management, sibling interactions, adult behavior, leisure time activities, and such problem areas as violence, drug abuse, and early pregnancy).

Major Findings: In general, the post-1973 studies have been consistent with earlier work in concluding that members of smaller families tend to fare better than members of larger families across a broad range of life outcomes. The more recent work has, for many outcomes, been especially persuasive because of the use of more sophisticated research and sampling designs and analytic strategies than was true of earlier research. There is particularly strong evidence that children from smaller families are advantaged with respect to intellectual performance, academic achievement, and, as adults, occupational prestige, even when their social class or origin is controlled. Research on children's personality, mental health and behavioral problems is less conclusive. However, there does appear to be reasonably solid evidence refuting the "only-child" stereotype of maladjustment, loneliness, and dependency. In the past decade there has been considerably more interest in the effects of family size on parents, and this work also tends to favor small families. Of particular note is the economic research that has estimated the financial costs, including opportunity costs of children. Research on family size since 1973 is characterized not only by increased methodological rigor but also greater theoretical development.

Significance to Biomedical Research and Program of the Institute: Given current interest in effects of family size, and anticipated increase in research on this topic, it is useful to the scientific community to have a comprehensive review of prior research, methodologies and results.

Proposed Course: This research is scheduled for completion in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Research on the Effects of Fertility on Changing Roles of Women and Men
Contract Number: N01-HD-12817
Contractor : Cornell University
Money Allocated: \$99,631 (1981); \$111,488 (1982)

Objectives: The first task of this research is to estimate a system of non-market activity hours equations for men and women using predictors that include number and ages of children. The data for estimating activity functions will be the multi-state time use data collected by the North Eastern Experiment Station Regional Project (NE-113), and the Michigan Time Use in Economic and Social Accounts (TUESA) survey. The coefficients for the impacts of the configurations of children's ages will provide the desired information of time allocation effects of having and rearing children. However, the main goal of this task is to understand the impact on time in nonmarket activities. To attach a monetary value to the observed changes requires an estimate of the home wage. This shadow wage is the labor market reservation wage; any market wage offer above it will lead to employment.

The second major phase of the work is to estimate the effect of the differences between desired and actual number of children on additions to the stock of home and market skills. The respective proxies for these skills changes will be longitudinal differences in home and market wages. The main data base for this effort will be the 1968-1972 years of the Michigan Panel Survey on Income Dynamics (PSID). A stock-adjustment portfolio model is posited whereby prior differences between desired and actual stocks of skills, consumer durables, assets, and children influence current adjustments in these stocks.

It is emphasized that it is of particular interest how the effects of fertility operate on the wives' acquisition of home and market skills. A third phase repeats the two main tasks for single parents. Three data sets will be used--single parents from California in NE-113, the single parents in TUESA, and single parents in the PSID.

Significance to Biomedical Research and Program of the Institute: The research is important for its explicit recognition of the role of fertility desires in the acquisition of home and market skills.

Proposed Course: This research is expected to continue through FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : The Effects of Fertility on Changing Roles of Women and Men
Contract Number : N01-HD-12818
Contractor : University of North Carolina
Money Allocated : \$228,543 (1981); 205,120 (1982)

Objectives: A simultaneous equations model of time allocation to market work, child care, housework, and leisure activities by men and women will be estimated for couples. This model will estimate the extent that shifts in activities of one spouse constrain or complement shifts in the other spouse's activities, each responding to changes in predetermined numbers and ages of children. Related analyses will determine the impacts of the spacing and timing of births, and of the prior labor force attachment of the woman. The data sets for this estimation are the 1974-1976 Time Use in Economic and Social Accounts data and the longitudinal Utility Study of urban couples for 1974-1979.

Couples may treat the husband's and wife's time as imperfect substitutes in childrearing activities. However, if sex roles change, the impact of this may affect the response of couples' time allocation to their births, as well as condition the effects of other important predetermined variables, such as the wife's market wage. To obtain correct projections of variables, the opportunity costs of children, the research team will attempt to determine how sex-role change might alter the distribution of activities between wives and husbands. To obtain the information to forecast sex-role changes, this team will study differentials in activity shifts between men and women that cannot be explained by the predictors in the two-sex model.

The final phase of the research is to estimate part of the indirect effect of children (via labor force intermittency) on market wages. One way in which intermittency reduces wage rates is through skill deterioration. These effects will be estimated with the National Longitudinal Survey and the Panel Study of Income Dynamics.

Major Findings: In the application of econometric methods to the study of wage rate attrition as a cost of fertility, preliminary regressions of wage rate on explanatory variables such as years of education, experience, home time, and part time work indicate that education and experience each have positive and significant coefficients on wages.

Significance to Biomedical Research and Program of the Institute: This research is expected to clarify the impact of childrearing on demands on the time of men and women and their decisions to rear children.

Proposed Course: This research is expected to continue through FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Effect of Parenthood on Activities of Young Adults
Contract Number : N01-HD-12819
Contractor : The Rand Corporation
Money Allocated : \$124,448 (1981); \$127,168 (1982)

Objectives: The research will examine the effect of parenthood on the lives of young men and women, using data from the National Longitudinal Study of the High School Class of 1972. Initial interviews were conducted in 1972 and four follow-up surveys were administered to a sample of more than 20,000 members of the graduation cohort with the most recent in 1979. The research would focus on how parenthood affects (1) educational patterns, (2) labor force participation, (3) career patterns, (4) economic well-being, (5) community and political participation, and (6) allocation of time to various activities. Relatively homogeneous groups of respondents will be treated on the basis of sex, parity, and timing of marriage and parenthood for various parts of the analysis. Actual behaviors, as well as aspirations, will be examined, as will outcomes for both men and women. The analysis will focus on two types of comparisons: (1) activities and aspirations of individuals after becoming a parent with those of the same individuals before parenthood; and (2) activities and aspirations of parents and non-parents at comparable periods of their lives. The analyses will group respondents by sex, parity, race, age at marriage, age at first birth, spacing, and socioeconomic status. Parenthood effects will be inferred from comparing changes in group means of effect variables over time and across groups, adjusting for background factors and experiences that also influence activities.

Significance to Biomedical Research and Program of the Institute: The broad areas of outcomes identified as effects of parenthood on youths should be of great interest to both policymakers and parents.

Proposed Course: This two-year project will be completed in FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : The Opportunity Cost of Rearing American Children
Contract Number : N01-HD-12820
Contractor : The Urban Institute
Money Allocated : \$124,749 (1981); \$168,220 (1982)

Objectives: The objective of this research project is to estimate total opportunity expenditures on children, defined as the value of parents' time withdrawn from the labor market due to the presence of children. To this end two calculations are required: 1) the differential in parents' time spent at work and not at work by presence of children, and 2) the monetary value of the hours subtracted from or added to market work. For the first, multistate life table techniques are applied to longitudinal work history data from the National Longitudinal Surveys to represent in a compact way how much of observed cohort lifetimes can be expected to be spent in each of several mutually exclusive employment statuses (e.g., not at work, at work part-time, at work full-time). Separate multistate increment-decrement life tables will be computed for each parity class so that the effect of an additional child on time spent at work by single years of parents' age can be estimated. For the second calculation, the opportunity price of time will be estimated from earnings functions formulated by Mincer and expressing hourly earnings as a function of participation and nonparticipation in the labor market and other variables. The product of the quantity of time lost from market work attributable to children and the marginal price of time yield an estimate of opportunity expenditures. In the last part of the study, the opportunity cost of a child born in 1980 will be projected through the age of financial independence and beyond.

Significance to Biomedical Research and Program of the Institute: This research is likely to greatly advance understanding of the effect of childbearing on the amount of time lost from market work and displays substantial promise for increased understanding of the total impact of childbearing.

Proposed Course: This three-year project is expected to run through FY 84.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Research on the Effect of Fertility: A Time Series Analysis of
the Opportunity Cost of Children
Contract Number: N01-HD-12821
Contractor : Mathematica Policy Research, Inc.
Money Allocated: \$73,010 (1981); \$85,146 (1982)

Objectives: The study will focus on the effects of childbirth on the market earnings of both parents. The investigator will adopt a time-series perspective and do the following: (a) set up a cohort model of human capital accumulation by working with "longitudinal" data sets of age-order specific birth rates, age-order specific cumulative fertility, and age-specific labor force participation rates over the 1947-1978 period; (b) examine time-series relationship between wage rates and human capital accumulation; (c) analyze both direct (via participation rate) and indirect (qualitative, via change in human capital) and thus wage rate effect of childbirth and child spacing on labor supply; and (d) make projections of the effect of fertility.

Significance to Biomedical Research and Program of the Institute: This research is important in its attempt to specify a time-series model of opportunity costs of children.

Proposed Course: This two-year project will be completed in FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : The Effect of Fertility Decisions on Pecuniary and Nonpecuniary
Compensation
Contract Number : N01-HD-12822
Contractor : Mathematica Policy Research, Inc.
Money Allocated : \$83,000 (1981)

Objectives: The proposed project will assess the effects of having a child or an additional child on the job compensation of parents, focusing on changes in wages and other job compensation of parents associated with having children. Separate calculations will be made by number of children, birth order of child, and race and ages of parents. The data for the analysis will be drawn from the National Longitudinal Surveys of Young Men and Young Women which provide detailed data on employment, marital, and fertility behavior for several thousand young people over a 15-year period.

Significance to Biomedical Research and Program of the Institute: The findings of this research should add to our understanding of the economic consequences of having children.

Proposed Course: This research will be completed in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Social-Demographic Aspects of Delayed Childbearing
Contract Number : N01-HD-12823
Contractor : University of North Carolina
Money Allocated : \$63,492 (1981); \$112,083 (1982)

Objectives: This research involves a three-year study of a wide variety of different aspects of delayed childbearing. The project consists of six separate, though related, research projects, most making use of different data and each inquiring into a different aspect of delayed fertility. The project examines aggregate vital statistics data and published historical data on a variety of social, economic, and demographic variables in order to ascertain the aggregate interrelationship between these variables and the proportion of a given birth cohort childless at given ages (25, 30, and 35). The second study involves using 1975 and 1980 June Current Population Survey data and the GAF, NFS, and NSFG surveys to investigate the influence of a variety of socioeconomic variables (including color, region, farm background, religion, education, husband's occupation, etc.) on the tendency to remain childless by ages 25, 30, and 35. The third study involves using the same data sets as the second to investigate the variables that discriminate between those who remain childless and those who bear a child, given the postponement of fertility to a certain age. The fourth study endeavors to estimate causal models of age at first birth as affected by (and affecting) education, as well as a wide variety of exogenous variables relating to background, adolescence and biological factors. The fifth study uses the National Longitudinal Survey of the High School Class of 1972 (NLS) to investigate the relationship between alternative career paths and delayed fertility. The emphasis is upon tracking the manner in which movement into certain career lines, particularly an academic path, influences the postponement of fertility. The sixth and final study also relies on the NLS data to inquire into the success with which the respondents in this longitudinal survey were able to predict their fertility patterns between the ages of about 22 and 25.

Major Findings: The rapid increase in the number of first births occurring to women over 30 is due to postponement of births at younger ages. Dominant are period factors, which may include housing, job markets, or political events. Among Blacks, there has been a decline in the proportion reaching 30 childless, but the probability of subsequently giving birth has increased.

Significance to Biomedical Research and Program of the Institute: This research builds on the previous analyses and, linked together, will form a coherent whole to paint a detailed picture of delayed childbearing during this century.

Proposed Course: This project is expected to run through FY 84.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Research on Delayed Childbearing
Contract Number : N01-HD-12824
Contractor : Carnegie-Mellon University
Money Allocated : \$53,294 (1981)

Objectives: The central objective of this research is to study aspects of delayed childbearing with the aid of theory-based, empirically tractable models of cohort fertility by birth order. A first phase will be to develop and test models for cohort age distributions of first birth frequencies and estimators for the models, and then to model the effect of period fertility on cohort first birth fertility. This phase will evaluate the Coale-McNeil marriage model as applied to first births. Subsequently, the investigator will analyze and compare first birth fertility patterns of cohorts of white and nonwhite women in the U.S. using National Center for Health Statistics (NCHS) data; study the determinants, and trends in the determinants, of delayed childbearing using fertility and socio-economic variables from the National Survey of Family Growth (NSFG) for 1973 and 1976; compare delayed childbearing in the U.S. with that in other developed nations; and evaluate the implications of delayed childbearing, teenage childbearing, and changing proportions of women who remain childless.

Major Findings: The proportion of women who will never have a first birth is increasing across cohorts and can be expected to be as high as 25 percent and 20 percent for recent white and nonwhite cohorts respectively. Recent nonwhite cohorts have an appreciable number of first births at earlier ages than their white counterparts as well as a lower mean age at first birth and increasingly less dispersion (across cohorts) in their age at first birth. The mean age at first birth and proportion of first births occurring between ages 25 and 34 is increasing across cohorts of white women but is stable across cohorts of nonwhite women.

Significance to Biomedical Research and Program of the Institute: This research is expected to contribute substantially to our understanding of fertility timing, changes in fertility timing, and international comparisons.

Proposed Course: This project will run through FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Research on Delayed Childbearing: The Determinants of Age at First Birth and Average Birth Interval
Contract Number : N01-HD-12825
Contractor : Mathematica Policy Research, Inc.
Money Allocated : \$73,625 (1981)

Objectives: This research examines the relationship between trends in the timing of childbearing and various social, economic and demographic factors. Two measures of fertility timing are used--median age at first birth and average interval between births. Socioeconomic factors considered are (1) shifts in median age at marriage for men and women; (2) increasing levels of educational attainment; (3) changes in employment patterns of women; and (4) changes in the relative economic status of young men. The hypothesis motivating the research is that over time, market earnings potential of sexes at the time of marriage has become more homogeneous, as reflected in narrowing differentials in age at marriage. This trend toward sexual equality in market productivity and earning power, in conjunction with variations in the relative economic well-being of young men, is hypothesized to have induced increased female labor force participation and delayed childbearing. Because childbearing and employment compete for women's time, increased earnings potential of women relative to men may affect birth intervals. Time series data from 1950 through 1977 is used to formulate and estimate a behavioral model of median age at first birth and average cohort birth interval to the measures of age, education, employment and economic well-being.

Major Findings: Empirical results from the 1950s suggest that a narrower age gap between husband and wife at first marriage is associated with increased earnings of females relative to males. However, the rate (female earnings/male earnings at first marriage) has been declining for recent cohorts. Although the age at first marriage has increased for both males and females, it has increased more for men than for women, leading to an increase in the age gap and earnings differential at first marriage in recent cohorts.

Significance to Biomedical Research and Program of the Institute: In an era of low and controlled fertility, issues related to timing become preeminent; this research explores reasons for the current delay in first birth.

Proposed Course: This project will run through FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Research on Delayed Childbearing
Contract Number : N01-HD-12826
Contractor : University of Iowa
Money Allocated : \$62,159 (1981); \$63,087 (1982)

Objectives: The aim of this research is an intensive analysis of first birth intervals, including delayed births, for successive cohorts of women who first married between 1950 and 1970, through the application of recent methodological advances to the multivariate analyses of life table relationships. These techniques will be used to provide basic descriptive information about the shape of first birth interval curves and also to analyze the influence of selected socio-economic and demographic correlates and determinants of first birth intervals. The data base will be the 1973 National Survey of Family Growth (NSFG) which included 7,644 women married less than three times and whose reproductive careers occurred during a period when first birth intervals shortened and then lengthened.

Major Findings: This study of sequencing and timing of first births utilizing life tables and proportional hazards models found that a sizeable minority of women became mothers either before or after a first marriage. Among Black women, marrying in the teens, lower education, broken parental homes, large number of siblings, nonuse of birth control and nonlabor force participation are all factors which promote the risk of a premarital birth. The percentage of marriages involving premarital birth is increasing. The pace at which first births occurred following marriage quickened during the 1950s and slowed during the 1960s, with a particularly rapid decline in 1965. Factors related to a rapid pace at first childbirth after marriage include young age at first marriage, lower education, nonuse of birth control, large number of siblings and no labor force participation. Once premarital conceptions are excluded, Black women have their first births at about the same pace as white women.

Significance to Biomedical Research and Program of the Institute: This research is expected to expand our knowledge about key factors associated with the likelihood of having a first birth after a specified marriage interval.

Proposed Course: The research will be in progress through FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : A Dynamic Model of the Expectations and Fertility of Childless Women
Contract Number : N01-HD-12827
Contractor : The Urban Institute
Money Allocated : \$139,550 (1981)

Objectives: Using a dynamic sequential decision-making approach, the investigators will examine variables which influence the timing of fertility and the consequences of fertility delay for later fertility, using a sample of currently married women from the 1971 and 1976 waves of the Panel Survey of Income Dynamics. Fertility will be examined in terms of: (1) the total number of children that childless women expect to have and (2) the probability that a woman will have a first birth during a particular time interval.

Major Findings: In studying decision making in delaying childbearing, a "fertility gap" is postulated. If economic variables change or if expected births fail to materialize, both expectations and subsequent behavior are modified, depending on the size of the gap and the time remaining for childbearing. For those couples expecting additional children in 1971, 44 percent had a child between 1971 and 1973; of those, 33 percent went on to lower their total fertility expectations by 1973. Of the remaining couples expecting more children in 1971 (i.e., those not having a child between 1971 and 1973), 46 percent lowered their total expectations by 1973. The results are more striking when a longer interval is considered--71 percent of the couples with unfulfilled expectations in 1973 experienced a birth between 1973 and 1978. Of those, only 26 percent lowered their expectations by 1978. In contrast, 65 percent of the couples with unmet goals who experienced no birth in that interval lowered their total expectations by 1978. These early findings suggest that unfulfilled fertility plans are constantly being evaluated and modified in response to changing circumstances.

Significance to Biomedical Research and Program of the Insititue: A particular strength of this research lies in its use of a sequential rather than a static model of fertility decision making, which should further our knowledge of the processes leading to delayed childbearing.

Proposed Course: This research will be completed in FY 82.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Childcare and Fertility Expectation, June 1982
Contract Number : Y01-HD-21052-00
Contractor : Bureau of the Census
Money Allocated : \$160,000 (1982)

Objectives: This project involves the addition of questions regarding fertility expectations and child care to the June, 1982 CPS. These data will be collected in conjunction with information about background sociodemographic characteristics, labor force participation, and household composition. In addition to the collection of data on fertility expectations and child care, the data will be cleaned and edited and a clean and documented data tape will be prepared. The data tape will be a deliverable and will also be made available through the Bureau of the Census for public use.

Data on fertility expectations will be collected of all women aged 18-44 and child care questions will be asked of those women with at least one child under the age of five. For employed women, the questions will cover information on child care used while they are working.

Significance to Biomedical Research and Program of the Institute: Up-to-date fertility expectations and child care are topics which are of basic concern to the Institute.

Proposed Course: This project is scheduled for completion in FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Puerto Rican Fertility Survey
Contract Number : Y01-HD-21054-00
Contractor : Center for Disease Control
Money Allocated : \$300,000 (1982)

Objectives: The research project will study fertility and family planning patterns among Puerto Rican women. The data base will include a sample of approximately 3000 women aged 15-49, and will be representative of the Puerto Rican population. The aims of the research are to 1) assess the interrelationships of life-events such as marriage, female employment, migration behavior and fertility, 2) estimate the extent of contraceptive use, and methods used, and 3) estimate needs for family planning in situations of unwanted fertility and the acceptability of methods of limitation.

Significance to Biomedical Research and Program of the Institute: This project will provide an important resource to the scientific community in that it will provide valuable data on contraceptive practices and fertility behavior. In addition, the project is using a life history approach to data collection which will allow for the study of the interrelationships between fertility and other major life events.

Proposed Course: This project is scheduled for completion in FY 84.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Social and Behavioral Sciences Branch
Contract and Collaborative Research

Contract Title : Computerization of Fertility Tables for Birth Cohorts by
Color: United States, 1917-1980
Contract Number : Y01-HD-21055-00
Contractor : Bureau of the Census
Money Allocated : \$16,000 (1982)

Objectives: The purpose of this project is to produce a computer data tape containing the 10 tables and sub-tables which comprise the book entitled "Fertility Tables for Birth Cohorts by Color: United States, 1917-1973" and updated with natality data through the year 1980. The project will build on the work already under way at the Census Bureau and will assemble the data that now comprise Table Number Four in the above-mentioned book. These data will then be converted to the other nine tables by use of the mathematical formulae contained in the appendices of the book and by adding data that will time-splice the tables to account for the fertility experience of the women under study accumulated to 1917. The verified and cleaned tape will be made available to the general public through the National Technical Information Service. Data tape will be provided as a deliverable to the Center for Population Research, NICHD, and it will be made available to the public through NTIS.

Significance to Biomedical Research and Program of the Institute: This project will make available to the scientific community a computer accessible form of data on fertility, a topic of central importance to the Institute.

Proposed Course: This project is expected to be completed in FY 83.

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Center for Population Research
Reproductive Sciences Branch

As a Branch of the Center for Population Research (CPR), NICHD, the Reproductive Sciences Branch (RSB) facilitates the acquisition and application of the knowledge required to enable men and women to: 1) regulate their fertility; 2) overcome their infertility; and 3) alleviate or cure their reproductive diseases and disorders. The primary means by which such facilitation of the CPR mission is accomplished by the RSB is through the award of grants for the support of research and training in the reproductive sciences. During the period from October 1, 1981 to September 30, 1982, RSB provided funding for grants and other forms of support for activities subsumed by the following programs: 1) Fundamental Biomedical Research on Problems of Human and Relevant Animal Reproduction; 2) Institutional Programs in Multidisciplinary Reproductive Sciences Research; 3) Reproductive Sciences Research Manpower Development; and 4) Reproductive Sciences Research Facilitation and Augmentation.

1. Fundamental Biomedical Research on Problems of Human and Relevant Animal Reproduction

A. Reproductive Biology

Regulation of Testicular Androgen. Studies of various steroidogenic enzyme activities related to testicular testosterone production have been undertaken to increase understanding of factors involved in the formation of this important androgen and the factors, particularly the pituitary luteinizing hormone (LH), involved in its regulation. Evidence has been obtained that the structural components of the testes, the Leydig cells and the seminiferous tubules, appear to contain two forms of an enzyme, 17-ketosteroid reductase, which catalyzes the final step in the biosynthesis of testosterone. The testes of rats have been shown to contain three distinct populations of Leydig cells which differ in their capacity to produce testosterone. Changes in the number of Leydig cells in each population have been found to occur at times when androgen levels change during sexual maturation. This shift in types of Leydig cells may be a cause of the increase in testosterone production seen in response to the stimulus of LH that occurs during sexual maturation. Increased knowledge of the various enzymes involved in testosterone biosynthesis has relevance both to the understanding of normal testicular function and to possible new approaches to the alleviation of male infertility.

Luteolysis in the Primate. The mechanisms of luteolysis in the primate, including the human being, are poorly understood and cannot readily be ascribed to hypothalamic pituitary regulation. In most nonprimate mammals, luteolysis has been attributed to the uterine synthesis and release of prostaglandins. However, the mechanism is not operable in primates as hysterectomy does not alter cyclic ovarian function in women or monkeys. Studies now show for the first time that prostaglandin F₂ alpha is luteolytic in the primate at physiological levels when administered intraluteally. Further, the luteolysis appears to be a functional one in that the hormonal events are compatible with those observed in normal, spontaneous luteolysis and there is a structure-function relationship. Corpus luteum size and progesterone production decrease, and the response of the tissue to exogenous gonadotropin and cyclic nucleotide appears to be similar to normal events. It would appear that functional luteolysis in the primate is an event that commences and is executed by the corpus-bearing ovary and that prostaglandin F₂ alpha of ovarian and

possible corpus luteum origin may be directly involved with luteal demise. These studies increase our understanding of the mechanisms of luteolysis in the primate and may be correlated to events in women. They have relevance to reproductive diseases and disorders manifested by defective luteal function and infertility.

Oviductal Secretions and Fertilization. Oviductal secretions contribute to the environment in which sperm capacitation, fertilization, and early embryo development occur. Recent work has shown that major macromolecular secretions of the oviduct are sulfated. Studies of the hormonal control of these secretory products of the oviductal epithelium indicate that they are dependent upon estrogen stimulation. Evidence has now been obtained for the localization of these glycoproteins within oviductal tissue (ampulla, the ampullar--isthmic junction and the isthmus) and it suggests that secretory granules within all regions of the oviduct do not contain similar components. These findings indicate that specializations within regions of the oviduct may be responsible for specific functions of the oviduct in the critical events of fertilization and embryo development.

Fetal Antigen Immunization and Reproductive Consequences. The immune response of two antigens (F9 and ENDO) has been studied. These are present on fetal tissues but absent from normal, adult, somatic tissues of mice. These antigens are, however, present on mouse sperm, early embryos and teratocarcinomas. The results obtained show that multiparous (many births) females and vasectomized males both have detectable serum antibodies to F9 and possibly ENDO. These results suggest that the inhibition of fertilization and early embryo development which occurs following the mating of female mice immunized to F9 could happen in a natural setting, i.e., an infertility circumstance. In addition to a potential role in infertility, these results suggest the possibility of immune prophylaxis of pregnancy in man.

B. Reproductive Biochemistry and Molecular Genetics

Internalization of Gonadotropins. The mechanisms of action of gonadotropic hormones are of major importance in the reproductive sciences. Progress has been made in characterizing the biochemical and physical properties of these mechanisms of action of the luteinizing hormones. The first studies are reported of free biologically active hCG within its target cell. In producing its effects on its target cell, gonadotropin appears to be "internalized" into the cell and this process is accompanied by marked alteration of its carbohydrate component. After internalization, hCG remains biologically active for unexpectedly prolonged periods and this raises the possibility the hCG may be internalized to induce specific subcellular biochemical effects in addition to undergoing degradation. This new knowledge of the mechanisms of action of the gonadotropic hormones increases our understanding of normal reproductive processes and, thus, allows better rationales for alleviation of reproductive diseases and disorders as well as for development of new methods for fertility regulation.

Estrogen Control of FSH. The regulation of gonadotropin secretion by gonadal estrogen has relevance to many reproductive processes and events. Utilizing an ovine pituitary cell culture, a RSB grantee has made the significant demonstration that estrogen decreased pituitary production of FSH by decreasing mRNA levels for the FSH beta subunit. This is important because it suggests that estrogen controls FSH transcription directly at the gene. Preliminary data indicate that the human male pituitary responds to estrogen in a manner similar to that of the sheep pituitary. In increasing our knowledge of the mechanisms of action of estrogens in

regulating gonadotropin secretion, this work has positive implications for the alleviation of certain diseases and disorders of the reproductive tract.

Male Transmitted Lethal Gene Affects Implantation. A major breakthrough has been reported in sorting out the arrangement of abnormal forms of genes in a region of chromosome 17 of the mouse. Groupings of these gene forms, called t-haplotypes, are associated with early embryonic death, abnormal maturation and function of male germ cells and certain anatomical defects. The new technique consists of using parental gene lines carrying several specific gene forms that permit the successful mixing (recombination) of other gene forms within the T/t complex grouping (haplotype). Experiments completed so far have shown for the first time that the different lethal t-maturations (gene forms) appear to be members of a multigene family spread out over a defined region (20 centimorgans long) of chromosome 17. Furthermore, using genetic techniques called recombination analysis and deletion mapping, two new mutations have been discovered within the tw73 haplotype. One causes death in neonatal mice (within 24 hours) due to abnormal lipid levels in the blood. The second is an early embryonic lethal that affects the implantation of the embryo in the uterus. These mutations are called "parasite" mutations because they are apparently spontaneous mutations unrelated to the conventional t-lethal factors. They were not previously known because they have remained associated with the t-haplotype region and were isolated from natural selection by their residence on an already lethal chromosome with high rates of transmissions through males. These findings indicate the existence of a genetically transmitted male factor that directly influences the mechanism of embryonic implantation in mammals.

Gonadotropins: Gene Structure and Regulation. Using recombinant DNA technology, the amino acid sequence of the rat pre-alpha gonadotropin subunit (common to LH and FSH) has been determined. The rat DNA sequences of the two largest (cloned DNA) inserts (segments) encoding the pre-alpha subunit were identified and analyzed. The amino acid sequence was deduced by translating the DNA sequence code. The composite sequence determined spans 610 base pairs or almost the entire length of the transcribed messenger RNA (800 base pairs). The rat alpha precursor subunit consists of a 24 amino acid leader sequence and a 96 amino acid alpha subunit apoprotein. The rat sequence has significant amino acid and nucleode homologies with the mouse and human. The cloning of the DNA probes coding for the rat pre-alpha subunit represents a significant achievement. These probes will permit the study of the organization and regulation of the genes encoding the subunits of the glycoprotein hormones. It appears that a major advance in our knowledge of gonadotropin gene structure and function is imminent.

Transfer and Inheritance of a "Working" Gene. The successful transfer of a "working" gene from one species to another and its inheritance by offspring has been achieved. The DNA region containing the promotor/regulatory region of the mouse metallothionein (MT) gene was experimentally fused to the Herpes Simplex virus structural gene for thymidine kinase (tk) using recombinant DNA technology. The experimentally constructed gene (fusion plasmid) was then injected into the male pronucleus of fertilized mouse eggs. The injected eggs were introduced into the oviduct of surrogate mothers. About 10-15 percent of the offspring carried the foreign gene and many of them expressed high levels of viral thymidine kinase in their liver. The tk activity was found responsive to the inducer of the MT gene (cadmium). These transferred genes have been shown to be inherited by offspring of the mated "carriers." The expression in such offspring is, however, incompletely stable. It is subject to modification by molecular events not yet understood. Examples of MT gene expression extinction, reduction, and enhancement have been

observed in offspring relative to their parent. The liver MT gene studied has several important characteristics. It is responsive to estrogen, inducible by cadmium, and produces a known protein product. This product (metallothionein) is a ubiquitous protein in animal cells that should respond to normal cell signals. This system should provide an excellent model in which to study the effect of differentiation on gene expression.

New Prostaglandin Analogs. In recent years, there has been considerable interest in the possible pharmaceutical use of prostaglandins as luteolytic agents for the control of fertility. Currently, the smooth muscle stimulating side effects (nausea, vomiting, diarrhea) that occur with pharmacological doses of natural prostaglandin-F₂-alpha (PGF₂-alpha) limits its clinical potential. Recently, however, the chemical synthesis of a series of potentially useful PGF₂-alpha analogs has been accomplished. These new fluoroprostaglandins are methyl esters in which fluorine replaces protons in the structure of PGF₂-alpha. The new analogs evidence significant luteolytic activity with only negligible smooth muscle stimulating activity. The results achieved not only indicate a possible contraceptive use of these analogs, but also suggest they may be useful in determining the role of prostaglandins in certain types of infertility and dysmenorrhea.

Progesterone Regulation of Estrogen Action. A significant advance has been reported in our understanding of the molecular mechanism of steroid action. The steroid hormone progesterone is known to physiologically modulate the action of another steroid hormone (estrogen) by regulating the retention of estrogen receptors in the nucleus of uterine cells. In a recent study of the relative nuclear content of receptors with estrogen attached (occupied) and receptors without estrogen attached (unoccupied), progesterone caused a preferential and accelerated loss of occupied estrogen receptor complexes. This preferential loss is thought to be associated with an estrogen receptor complex releasing factor induced by progesterone. One exciting new finding is that the releasing factor activity is inhibited by types of inhibitors that affect phosphatase enzymes. A series of studies appear to rule out alkaline phosphatase involvement but inhibition curves showing a correlation to acid phosphatase activity have been obtained. Furthermore, measurable increases in nuclear acid phosphatase activity have been shown to be induced by progesterone. These results demonstrate for the first time a unique progesterone-induced releasing activity which acts selectively on the occupied form of the estrogen receptor. This releasing factor currently appears to be an acid phosphatase. These findings are of great potential significance in understanding the mechanism of action of steroid hormones. Since the occupied estrogen receptor complex is widely believed to stimulate the hormone-dependent gene expression producing the unique biological activities of the target tissue, it would now appear that this mechanism may be modulated by progesterone regulation of the nuclear retention of such complexes. Furthermore, the results suggest the novel and exciting possibility that the mechanism of estrogen action may actually be controlled enzymatically by a dephosphorylation mechanism.

Protease Inhibitor Protection of the Pregnant Uterus. In response to stimulation by progesterone, the uterus of the pig secretes a group of small sized molecules which inhibit enzymes (proteases) that break up proteins. One of these molecules, called a protease inhibitor, has been isolated and biochemically characterized. It very strongly binds (one to one) with only three particular enzymes (trypsin, chymotrypsin and plasmin). It does not bind any other protease tested. Antiserum raised against it produced antibodies used to make immunological tracers that allowed its location in tissues to be studied. The inhibitor was only associated with uterine

glandular and surface (epithelium) cells. Since the antiserum also reacted with three other small sized molecules that inhibit trypsin and plasmin, the results suggest the existence of a family of similarly structured inhibitor molecules that may constitute up to 15 percent of the total protein in the uterine secretion of the pig. The inhibitor(s) apparently forms a protective coat on (and are taken up by) embryonic cells (trophectoderm) during pregnancy. It appears that the inhibitor(s) may represent a mechanism to both prevent the degradation of proteins essential to the growing conceptus and to protect the uterus from damage by proteases secreted by the conceptus.

Monoclonal Antibody to Progesterone Receptor. The biological function of the steroid hormone progesterone is to prepare the uterus for the reception (implantation) and development of the fertilized ovum. This it does by inducing the proliferated target cells of the glandular tissue to produce secretions essential to the survival of the early embryo. The mechanism of action of progesterone is critically dependent upon the successful binding of the hormone to specific biological molecules (called receptors) in the tissue. Progesterone receptors play a significant biological role in pregnancy, certain cancers, development, and aging. Research on progesterone receptor variations related to disease and dysfunction has, until recently, been impeded by the lack of stabilized receptor preparations with which to prepare immunological reagents permitting the rapid identification and quantitative measurement of receptor levels in tissues. Such research might, for example, help clarify why there is such a high rate of human embryo loss during the first few weeks of pregnancy. Using newly developed technology that stabilizes the progesterone receptor for isolation and purification, the subunit structure of the mammalian progestin receptor system has been clarified. At least five receptor forms of different sizes comprise the system. These are interconverted through a series of equilibria reactions. The smallest molecular weight form is called 3.5S while the largest is called the 8.5S receptor. This novel system may possibly be a universal steroid receptor model. The exciting finding is the reported routine isolation of the 8.5S receptor in microgram quantities. This has permitted the development of a hybridoma cell line which produces monoclonal antibodies directed against the 8.5S rabbit uterine progestin receptor. The IgG class antibody is specific for the progesterone receptor and is available in large quantities. This new immunological reagent should permit significant advances in our knowledge of the role of the progestin receptor in uterine function and dysfunction.

C. Reproductive Endocrinology

Control of FSH. The role of the ovarian peptide, folliculostatin, in the control of FSH secretion has been further defined. It has recently been shown that an antagonist to GnRH in ovariectomized rats suppresses serum LH by 90 percent while serum FSH is decreased by only 60 percent. This suggests that while LH secretion is highly coupled to GnRH, a considerable fraction of FSH secretion is independent of GnRH. In addition, it has been demonstrated that porcine follicular fluid can suppress GnRH-stimulated FSH secretion but not LH secretion in vivo. Studies to examine the ability of porcine follicular fluid to suppress the GnRH-independent component of FSH secretion show that in the absence of GnRH stimulation, porcine follicular fluid can selectively suppress FSH. These new data, along with previous observations, suggest the existence of a mechanism of FSH release which is independent of GnRH and steroid negative feedback but is susceptible to negative feedback by folliculostatin. In contrast, LH secretion is dependent on GnRH, very sensitive to steroid negative feedback and unresponsive to folliculostatin. These

differences in response of the two gonadotropins may underlie the mechanism by which LH and FSH are differentially controlled.

Cryopreservation of Endocrine Cells. Cell culture systems have been widely used for the studies of endocrine cells such as hormone secreting cells of the ovary and testis. To minimize trauma the cells are generally utilized within a short time of recovery from living tissues. This necessitates timely preparation of other experimental conditions. The time limitation sometimes results in inadequate utilization of the obtained cells. It is ideal if one can preserve endocrine cells and use them whenever necessary. Recently, RSB grantees have succeeded in preserving endocrine cells stored for several weeks at -90°C without loss of viability or responsiveness. When frozen granulosa cells were thawed and cultured, they behaved in a similar way to freshly harvested cells. FSH added to the culture medium significantly stimulated binding of hCG to these cells and increased secretion of progesterone. During a nine-day culture period, the protein content of the frozen/thawed cells increased three times. These parameters clearly indicate that ovarian granulosa cells can be stored frozen and can be utilized for experiments. This new methodology will facilitate greatly research on endocrine cells from human tissues.

Direct Inhibition of Human Ovary by LHRH Agonist. It has been shown that luteinizing hormone releasing hormone (LHRH) and its agonists can exert inhibitory effects on ovarian steroidogenesis *in vivo* and *in vitro* in the rat. It has not been as yet clarified as to how LHRH and its agonists exert their inhibitory effects. These hormones, when administered in large doses for a prolonged period of time, may excessively stimulate the anterior pituitary gland and result in abnormal secretion of gonadotropins, and thus indirectly disturb normal ovarian steroidogenesis. On the other hand, LHRH and its agonists may also act directly on the ovarian cells and inhibit steroidogenesis. In order to find out whether or not LHRH and its agonists inhibit ovarian steroidogenesis in the human being, and to determine whether they have direct effects on human ovarian cells, an LHRH agonist and an antagonist were tested for their ability to inhibit progesterone secretion by cultured human granulosa cells. When granulosa cells were harvested from large follicles during the late follicular phase and cultured with an LHRH agonist at relatively low concentrations, steroid production by the granulosa cells was inhibited. An LHRH antagonist had no marked effect on progesterone production, but it negated the inhibitory effect of the agonist. These results indicate that LHRH-like substances can directly influence ovarian cell function in the human being and that some LHRH agonists may act directly on the ovary.

Human Fetal Kidney Secretes hCG. Detection of human chorionic gonadotropin (hCG) has widely been used as a method of pregnancy test. This hormone is known to be synthesized and secreted by the placenta. Since the placenta can secrete hCG at its very primitive states (soon after implantation of blastocyst), it is of great interest from a developmental biological point of view to study the differentiation of trophoblastic cells and somatic cells in terms of capability to secrete hCG. When placenta and fetal organs were incubated separately, both placenta and fetal kidney were found to synthesize hCG whereas synthesis was not observed in fetal lung or muscle. Small, but significant, synthesis was also observed in the fetal liver. These observations constitute the first evidence that the genome of a fetal tissue directs the synthesis of what is considered a placental hormone.

Role of Catecholestrogen in Ovum Implantation. Preimplantation rabbit blastocysts have aromatase activity and can convert testosterone to estrogen. However, only a fraction of the estrogen formed is estradiol. It is, therefore, suggested that

other estrogens such as estrone, estriol or catecholestrogens may be formed. There is evidence that prostaglandins (PGs) are involved in ovum implantation. Since the endometrial levels of PGs at the site of implantation are significantly higher than those of interimplantation sites, and since removal of blastocysts results in a rapid decline in the PG levels at the implantation sites, blastocysts are likely to be the major source of PGs at the implantation sites. When blastocysts are incubated in vitro with estradiol or catecholestrogens and their effects on PG production by blastocysts are studied, catecholestrogens, but not estradiol, stimulate PG production. In another study using the mouse system, catecholestrogens abolish the delay in implantation of the ovum. These results suggest that, if the blastocyst or the endometrium has the capacity to convert estrogens to catecholestrogens, the PGs produced by blastocysts at the time of implantation are likely stimulated by catecholestrogens.

D. Reproductive Medicine

Amenorrhea/Hyperprolactinemia. The roles that disorders of prolactin secretion have in infertility are being studied in a number of laboratories. The increase reported in the diagnosis of pituitary microadenomas in women with amenorrhea/galactorrhea is probably related in part to technological advances in hormone measurement and x-ray methodology and to more effective means for both medical and surgical treatment. Whether a possible clinical association between diagnosis of these lesions and prior use of estrogen, usually in the form of oral contraceptives, really is valid is under investigation. A recent report in the literature of decreased bone density in patients with hyperprolactinemia has been confirmed in a study designed to determine whether the decreased bone mineral was specifically related to an elevation of prolactin or to decreased estrogen. Radius bone mineral was measured in normal women, in women with secondary amenorrhea who have normal serum prolactin, and in women with prolactin secreting pituitary tumors. The results suggest that hyperprolactinemia per se is associated with decreased bone mineral independent of sex steroid hormone concentration. In addition, the decrease in bone mineral is not rapidly reversed after successful transsphenoidal surgery. This finding is supported by a study in rats showing a direct effect on calcium resorption from bone. Further confirmation of bone mineral loss in hyperprolactinemic patients would provide a rationale, now lacking, for early medical or surgical treatment of patients with the amenorrhea/hyperprolactinemia syndrome.

Concomitant Release of LH and Prolactin. The observation of concomitant release of luteinizing hormone and prolactin in response to exogenous gonadotropin releasing hormone has lead to an examination of the possibility that simultaneous pulses of these two pituitary hormones may occur. Studies of normal women in the follicular and luteal phases of the cycle and of hypogonadal subjects show that the majority of prolactin pulses were associated with concomitant LH pulses. The frequency and amplitude of both LH and prolactin pulses were different in the three groups with the mid-luteal group having the greatest amplitude and the slowest frequency. Most of the hot flush episodes monitored in the hypogonadal women were found to be temporally related to simultaneous LH and prolactin pulses. These studies show a synchronized pulsatile release of prolactin and LH in normal cycling women and hypogonadal women and suggest that the ovarian steroid environment modulates the pulse frequency and magnitude of LH and prolactin.

Ovarian Follicular Disorders in Infertility. Information concerning two frequent causes of amenorrhea in infertile women, polycystic ovarian syndrome and premature ovarian failure has been obtained from studies of new methods of ovulation

induction. Preliminary data indicate that altered metabolism or excretion of FSH and LH may exist in some individuals with premature ovarian failure and suggest that abnormal species of FSH and LH may play a role in the development of this disease. Studies to date on polycystic ovarian disease suggest that the inhibitory effects of endogenous opioid peptides on LHRH release are functionally reduced. These studies of the pathophysiology of chronic anovulation in infertile women are increasing our understanding of follicular maturation and providing a better rationale for induction of ovulation in such women.

A Marker of the Defective Luteal Phase in Women. In response to progesterone, mammalian uterine cells produce and secrete products necessary for the biological functions of the uterus. There is marked interest at present in detecting and characterizing specific hormone-dependent uterine proteins which may play vital roles in pregnancy. Recent studies in women have revealed that the glandular lining of the uterus (endometrium) contains a protein whose synthesis is significantly increased during early pregnancy. There is an apparent direct relationship in cycling or pregnant women between their endometrial concentration of this protein and their serum levels of progesterone. This protein has been called PEP for Progesterone-associated Endometrial Protein. A significant advance has recently been achieved with the development of a very sensitive immunological assay using radioactive tracers (RIA) to quantitate the level of PEP in human endometrial tissues, amniotic fluids and sera. The results have shown that normally cycling women have a characteristic pattern of PEP levels during their cycle which differs from that observed during pregnancy and abnormal cycles. It appears that PEP is indeed a progestin-dependent protein and that serum PEP may be a very useful marker to monitor the cumulative effects of the hormone on the human endometrium. Although it is not yet known why PEP is there or what it is doing, its presence before implantation of the embryo and throughout early gestational development suggests that it has an important biological role. Of particular clinical importance is the potential of this new marker for evaluating the presence, extent, and therapeutic response of women with luteal phase defects, i.e., infertility therapy monitoring. In addition, PEP may be a sensitive and useful marker of pregnancy.

Treatment of Endometriosis. There is no medical treatment available for the treatment of endometriosis which can eliminate ovarian sex steroid production without requiring the use of pharmacologic amounts of steroids. A number of studies are now evaluating chronic administration of long-acting GnRH agonists to provide a temporary "medical oophorectomy" for women with endometriosis. Preliminary data from one study show that daily doses of the GnRH agonist (d-Trp⁶-Pro⁹-Net-LHRH or GnRH-A) for a month reduced serum levels of estrogens and androgens to those of oophorectomized women. After treatment, the subjects all reported either disappearance or improvement of the symptoms associated with endometriosis. Further studies are needed to determine the efficacy of this therapy, but it appears to be a promising approach to the alleviation of this reproductive disease.

Pelvic Inflammatory Disease and Chlamydia. Pelvic inflammatory disease (PID) is by far the most important complication of sexually transmitted diseases in this country. The long-term complications of PID result from the healing process. As the inflamed Fallopian tubes heal, they may become occluded, resulting in involuntary infertility and chronic pain. Although there is a tendency to consider PID as primarily an infection caused by Neisseria gonorrhoeae, recent studies indicated that there are other etiologies, e.g., Mycoplasma and Chlamydia. Chlamydia are small, round microorganisms that have a unique obligately intracellular developmental cycle that adversely affects the host tissues. Definitive studies regarding

the role of Chlamydia in PID and infertility have been seriously impeded by the lack of a suitable experimental model. Significant progress in establishing an animal model has now been reported. The ability to experimentally infect the uterus and Fallopian tubes of guinea pigs has been confirmed. A new and exciting finding is that the apparent resolution of the acute inflammatory process (within three weeks after inoculation) is followed by an accumulation of watery fluid in the distended uterine tubes of most of the animals. This condition, called hydrosalpinx, is similar to that observed in the human and is associated with infertility. The mechanism appears to be by a mechanical blockage of the ends of the Fallopian tubes. Thus, a potential model has been developed for studies of hydrosalpinx and infertility in which the induction of a fairly mild and resolved acute inflammatory process is followed by a serious consequence to the reproductive tract. This model may permit significant advances in our understanding of the role of Chlamydia infection and hydrosalpinx in infertility.

Inhibition of Gonadotropin Secretion by GnRH. Gonadotropin secretion can be inhibited by GnRH and some of its agonists and antagonists. Both agonistic and antagonistic GnRH analogs are being investigated as potential contraceptives for men and women. Fundamental information is needed on the modulation of gonadotropin secretion by these compounds. Preliminary studies in men to assess the inhibition of gonadotropin secretion by combined treatment with agonist and testosterone show that the combination inhibits gonadotropin secretion more effectively than agonist alone. The stimulation of gonadotropin and testosterone secretion by daily injections of the agonist in man is transient with inhibitory effects prevailing by day 10 of treatment. The combined therapy promises to predictably suppress spermatogenesis without impairing sexual potency.

FSH-Secreting Pituitary Adenoma. Serum concentration of FSH is elevated in most of the patients who have FSH-secreting pituitary adenomas. In these patients FSH secretion may be controlled in an abnormal fashion since FSH and LH levels are increased in response to TRH (thyrotropin releasing hormone) administration. The levels of LH and FSH are not influenced by TRH in normal subjects. When the pituitary adenomas extend into extrasellar areas, they interfere with normal vision. Transsphenoidal surgery of these patients resulted in marked reductions in adenoma size as judged by computerized tomography. Most of the patients who received the surgery showed declines in serum FSH concentrations into the normal range. The abnormal FSH and LH response to TRH was improved in all of the patients except one. These results indicate that the adenoma mass was directly responsible for all of the observed abnormalities of hormonal hypersecretion seen before surgery. The association of pituitary adenoma with selective FSH hypersecretion offers an unusual opportunity to study the control of FSH secretion, a subject that is crucial to understanding testicular function.

Pregnancy and DES Associated Genital Anomalies. Information has been obtained about the prevalence of upper reproductive tract anomalies in a patient population at risk for DES (diethylstilbestrol) induced anomalies of the cervix and vagina. These patients are adult females of child-bearing age who were exposed in utero to DES. Preliminary data on 267 DES-exposed women indicate that 69 percent of these women demonstrated an abnormality in the upper genital tract on hysterosalpingography (HSG). Ninety-three of the women on whom X-rays were performed had a total of 144 pregnancies. The pregnancy outcome on this group of women was significantly worse than that found in a control population. In addition, women with abnormal X-rays were found to have a poorer pregnancy outcome than the group of women with normal

HSG findings. Significantly fewer women with abnormal HSGs delivered term infants than women with normal X-rays. This study is continuing and accumulating additional cases.

Alleviation of Infertility in Men. The first successful cure of an infertile man by administration of synthetic luteinizing hormone releasing hormone (LHRH) has recently been confirmed by the birth of a child. This type of infertility in men has been very difficult to correct in the past. LHRH is a native hormone normally produced in the brain and it stimulates the pituitary gland to secrete gonadotropins which, in turn, stimulate the production of sperm by the testes. Administration of synthetic LHRH to men who have a deficiency of their own endogenous LHRH results in the synthesis and release of gonadotropins which can elicit the appropriate physiologic response in the gonads. A major breakthrough for the successful therapeutic use of this native hormone was the discovery of the necessity for its intermittent or pulsatile administration. A portable mini-infusion pump was adapted for the pulsatile delivery of LHRH which had to be administered over a period of many weeks. The basic knowledge needed for the practical application of hormone therapy was developed from studies in the nonhuman primate conducted over the past few years.

2. Institutional Programs in Multidisciplinary Reproductive Sciences Research

The RSB supports three types of Institutional Programs in Reproductive Sciences Research: Program Projects, Specialized Reproductive Sciences Research Centers and Reproductive Sciences Research Centers at leading institutions in the United States. Support for these programs is provided to enable such institutions to develop and to conduct reproductive sciences research programs involving such disciplines and such critical masses of highly skilled scientists as may be required for attacks on complex reproductive sciences problems that are beyond solution by the single investigator working alone or in relative isolation in his discipline. A total of 20 Institutional Programs were supported during the period from October 1, 1981 to September 30, 1982.

A. Program Projects

The recipient institutions and principal research areas of the Program Projects supported during the period from October 1981 to October 1982 are: 1) University of Pennsylvania - biochemical and biological events in reproductive processes prior to implantation; 2) University of Texas at Dallas - neuroendocrine and behavioral interrelationships; 3) University of California at San Diego - reproductive endocrinology; 4) Salk Institute for Biological Studies - neuropeptides in reproduction; and 5) Columbia University - chemistry of human chorionic gonadotropin.

B. Reproductive Sciences Centers

The recipient institutions and principal research areas of Reproductive Sciences Research Centers supported during the same period are: 1) Vanderbilt University - reproductive physiology and endocrinology; 2) Baylor College of Medicine - mechanism of hormone action; 3) Harvard University - reproductive biology and human reproduction; 4) University of Texas at San Antonio - reproductive mechanisms; 5) University of California at San Francisco - reproductive endocrinology; and 6) University of Pittsburgh - primate reproduction.

C. Specialized Reproductive Sciences Research Centers

The recipient institutions and principal research areas of the Specialized Reproductive Sciences Research Centers supported during the same period are:

1) University of Michigan - reproductive endocrinology from molecular to physiological levels; 2) Case Western Reserve University - reproductive biology of events from ovulation to implantation; 3) University of Texas at Houston - male reproductive function; 4) Mayo Foundation - mechanism of action and molecular biology of reproductive hormones; 5) Salk Institute for Biological Studies - neuroendocrinology of reproduction; 6) Columbia University - reproductive biochemistry and medicine; 7) The Oregon Regional Primate Center - events that control fertility in primates; 8) University of Washington - reproductive medicine and andrology; and 9) The Population Council - reproductive endocrinology.

3. Reproductive Sciences Manpower Development

Reduction in the number of trainees and rebudgeting by the institutions affected has been necessary to maintain the training programs.

A. Institutional Fellowships

The Institute awards grants for maintenance of institutional environments for research training in the reproductive sciences and for the support of both predoctoral and postdoctoral trainees selected for study in these environments. During fiscal year 1982, NICHD supported 24 reproductive sciences research training grants to 23 institutions. Of the 115 supported trainees, 52 were predoctoral and 63 were postdoctoral fellows.

In addition to these grants, two Professional Student Short-Term Research Training Grants were supported for 50 predoctoral students. This program is designed to expose talented students in health professional schools to the opportunities inherent in a research career in order to ease the projected shortage of clinical investigators in the future.

B. Individual Postdoctoral Fellows

In addition to institutional grants for research training, NICHD awards postdoctoral fellowships to individuals for the support of their training in research in the reproductive sciences. During fiscal year 1982, a total of 59 postdoctoral scientists were supported.

C. Research Career Programs

The Institute awards Research Career Development Awards (RCDA's) to outstanding senior postdoctoral candidates to enable them to devote full time to the development of expertise in research in the reproductive sciences. These awards provide salary to recipients for a maximum of five years support. In fiscal year 1982, 27 RCDA's were supported.

D. Clinical Investigator Awards

A new type of postdoctoral fellowship, the Clinical Investigator Award, was introduced in NICHD in 1981. This award affords the opportunity for promising, clinically trained individuals with demonstrated aptitude for research to develop

into independent biomedical investigators. It enables candidates to investigate, for up to three years, a well-defined problem with a sponsor competent to provide guidance in a chosen area of research in the reproductive sciences. During FY 1982, five Clinical Investigator Awards were supported.

E. Minority Biomedical Support

This program, administered by the Division of Research Resources, seeks to strengthen the biomedical research and research training capability of ethnic minority institutions in health-related sciences. The CPR contributed to this program by supporting two awards in the reproductive sciences.

4. Reproductive Sciences Research Facilitation and Augmentation

A. Conferences, Workshops and Symposia

Conferences, workshops and symposia are sponsored by RSB, CPR to facilitate the exploitation of new knowledge in critical areas of research in the reproductive sciences and to facilitate the rapid dissemination of new and significant information regarding the reproductive sciences. The following meetings were sponsored during the period from October 1, 1981 to September 30, 1982.

The fourth biennial workshop on the ovary, Regulation of Ovarian Function, was held in Madison, Wisconsin, July 17-19, 1982, at the University of Wisconsin. The workshop was chaired by Dr. Gilbert S. Greenwald, University of Kansas.

The Annual Meeting of Directors of CPR-supported Reproductive Sciences Centers and Program Projects was held in Rochester, Minnesota, August 18, 1982. It was hosted by Dr. Robert J. Ryan of the Mayo Foundation.

Following the Directors' Annual Meeting, a workshop on Monoclonal Antibodies: Applications to Reproductive Biology and Endocrinology was held in Rochester, Minnesota on August 19. It was sponsored by the Mayo Foundation and organized by Drs. Robert J. Ryan and Anthony Bellve.

A workshop on Expression of Cloned Genes in Development was held in Bethesda, Maryland, September 29-30, 1982. It was organized by Drs. Eric H. Davidson and William A. Sadler.

CENTER FOR POPULATION RESEARCH

Index to Project Reports

Contraceptive Development Branch

<u>Project #</u>	<u>Title</u>	<u>Page</u>
3-2741	A Study of the Use of Biodegradable Polymers for the Sustained Delivery of Contraceptive Drugs	20
5-2817	Development of a Long-Acting Injectable Contraceptive	21
7-2825	New Biodegradable Drug Delivery Systems	22
7-2826	Development and Testing of New Biodegradable Drug Delivery Systems	23
7-2829	Development of a Radioimmunoassay for Rhesus Monkey Luteinizing Hormone	24
7-2831	Development of Orally Active Dosage Forms for Steroids	25
7-2835	Folliculogenesis in the Rhesus Monkey during the Menstrual Cycle	26
8-2813	Biological Testing Facility	27
8-2815	Synthesis and Testing of Novel Steroids with Potential Male Contraceptive Activity	28
9-2838	Primate Testing Facility	29
0-2800	Clinical Pharmacology of LH/FSH-RH Analog	30
0-2811	" " " " "	31
0-2813	Synthesis of Luteolytic Agents	32
0-2816	New Antiprogestational Agents	33
0-2817	C-18 Functionalized Steroids	34
0-2818	Synthesis of Sulfur Analogs of Melatonin Derivatives	35
0-2819	Synthesis and Testing of Functionalized Polymers as Potential Contraceptive Agents	36
0-2828	Synthesis of New Potent Oral Antigonadotropic Agents for Male Fertility	37
0-2829	Synthesis and Testing of Male Contraceptive Agents: Gossypol Derivatives	38
0-2830	Peptide Inhibitors of LHRH as Ovulation Inhibitors	39
0-2831	" " " " " "	40
0-2832	" " " " " "	41
0-2833	" " " " " "	42
0-2836	" " " " " "	43
0-2845	Isolation and Purification of Rat Androgen Binding Protein	44
0-2847	Development of Microcapsules Containing a Contraceptive Progestagen	45
0-2854	Development of Hydrogel Materials as Vaginal Barrier Contraceptives	46
0-2855	Development and Testing of a New Cervical Cap and Inserter	47
0-2860	Isolation, Characterization and Synthesis of Gonadocrinin	48
1-2800	Development and Testing of Vaginal Contraceptives	49
1-2801	Development and Testing of Vaginal Barrier Contraceptives	50
1-2804	Use-Effectiveness Study of Cervical Caps	51
1-2807	Synthesis and Testing of Novel Steroids as Antiprogestational Agents	52

<u>Project #</u>	<u>Title</u>	<u>Page</u>
1-2808	Synthesis and Testing of Antiprogestational Agents	53
1-2809	" " " " " "	54
1-2810	" " " " " "	55
1-2811	Synthetic Chemical Facility	56
1-2828	The Development and Testing of New Spermicides	57
1-2829	" " " " " "	58
2-2807	Peptide Antagonists of LHRH as Gonadotropin Inhibitors	59
2-2808	" " " " " "	60
2-2809	" " " " " "	61
2-2810	" " " " " "	62
2-2812	" " " " " "	63

Contraceptive Evaluation Branch

Steroid Contraceptives--Cancer and Other Neoplasia		
7-2834	Secondary Amenorrhea, Pituitary Adenoma and Oral Contraceptives	69
9-2810	" " " " " "	69
9-2811	" " " " " "	69
9-2812	" " " " " "	69
8-1037	Oral Contraceptive Use and the Risk of Breast, Endometrial, and Ovarian Cancer	70
8-2803	Case-Control Study of the Relative Risk of Malignant Melanoma of the Skin Among Women on Contraceptive Steroids	71
8-2804	" " " " " " " "	72
Pathogenic Mechanisms		
0-2823	Research on the Presence of Abnormal Proteins in the Serum of Oral Contraceptive Users	73
0-2824	" " " " " " " "	74
1-2803	Longitudinal Studies of Lipoprotein Changes in Users of Various Oral Contraceptive Preparations	75
Vasectomy Projects		
6-2807	Health Status of American Men	76
7-2801	" " " " " "	76
7-2802	" " " " " "	76
7-2803	" " " " " "	76
8-2827	Effect of Bilateral Vasectomy on the Progression and Regression of Atherosclerosis in <u>Macaca fascicularis</u>	77
0-2806	Epidemiologic/Clinical Studies of Vasectomy and Atherosclerosis	78
0-2809	Epidemiological Study of Vasectomy and Coronary Heart Disease	79
0-2810	Study of Myocardial Infarction in Relation to Vasectomy	80
Birth Control and Infertility		
0-2821	Birth Control and the Risk of Infertility	81
0-2822	The Relationship Between Birth Control Practices and Occurrence of Subsequent Undesired Infertility	82

<u>Social and Behavioral Sciences Branch</u>		<u>Page</u>
6-2834	Fertility Values and Family Growth	103
8-2837	Adolescents' Perspectives on the Health Care System: A Determinant of Fertility	104
8-2836	Adolescents' Use of Information about Conception and Contraception: Cognitive and Interactive Processes Among Never-Married Female and Male Partners	105
8-2838	Research on the Determinants of Repeated Adolescent Pregnancy and Childbearing	106
8-2840	Sociosexual Development in Black Adolescents within the Family Context: A Longitudinal Study	107
9-2805	A Study of the Consequences of Deciding to Remain Childfree, Compared with Deciding to Have Children and Deciding to Postpone Children	108
9-2814	Research on Childlessness and the One-Child Family	109
9-2816	The Disruptive Effects of Fertility: A Longitudinal Study of the Sequential Consequences of Childlessness and Childbearing on the Educational and Occupational Pursuits of College-Educated Women	110
9-2819	Reciprocal Interaction Skills and Ego Identify Formation in Adolescents	111
9-2820	Sex Role Development and the Single Child Family	112
9-2821	Study of Consequences of Remaining Childless or Having Only One Child	113
9-2822	Societal Consequences of Adolescent Childbearing	114
9-2823	Estimating and Forecasting Money Expenditures on Children	115
9-2824	Estimating the Cost of Children in the United States	116
9-2825	Research on the Economic Determinants of Fertility	117
9-2830	The Consequences of Being and Having an Only Child on Intelligence, Interpersonal Orientation, Attitudes and Time Use	118
9-2835	Contraceptive Decision Making in Adolescent Couples	119
0-1045	Collection of Data in Cycle III of the National Survey of Family Growth Concerning Unwanted Childbearing and Contraceptive Practice in the Later Reproductive Years	120
0-2802	Contraceptive Decisions: Spousal Relationship, Method Commitment	121
0-2803	Interdisciplinary Assessment of Fertility Management in a High Fertility Community	122
0-2804	Consequences of Childlessness for Older Men	123
0-2837	Research on the Societal Consequences of Adolescent Childbearing Public Assistance Costs, 1975 and 1977	124
0-2838	Research on the Societal Consequences of Adolescent Childbearing	125
0-2849	Longitudinal Analysis of Family and Household Structure	126
0-2850	Changing Patterns of Marriage and Divorce in the United States	127
0-2852	Demographic Perspectives on the Consequences for Children of Changing Marital Patterns	128
0-2853	Changing Patterns of Household Structure: A Cohort Analysis	129

<u>Project #</u>	<u>Title</u>	<u>Page</u>
0-2857	Reproductive Behavior and Fertility Regulation among 20-29 Year old Unmarried Women	130
1-1048	National Longitudinal Survey--Adolescent Fertility and Family Formation	131
1-2138	Support of Bibliographic Preparation of <u>Population Index</u>	132
1-2802	Demographic Analysis of Family and Household Structure	133
1-2812	Household and Family Demography of Hispanics, Blacks and Anglos	134
1-2813	Patterns of Household Structure of the Elderly: Determinants and Future Trends	135
1-2814	Changing Living Arrangements and Family Formation of Young Adults	136
1-2815	Changes in the Structure of Central Appalachian Mountain Families and Households, 1900 to 1976	137
1-2816	Effects of Family Size: A Critical Review of Research Since 1973	138
1-2817	Research on the Effects of Fertility on Changing Roles of Women and Men	139
1-2818	The Effects of Fertility on Changing Roles of Women and Men	140
1-2819	Effect of Parenthood on Activities of Young Adults	141
1-2820	The Opportunity Cost of Rearing American Children	142
1-2821	Research on the Effect of Fertility: A Time Series Analysis of the Opportunity Cost of Children	143
1-2822	The Effect of Fertility Decisions on Pecuniary and Non-pecuniary Compensation	144
1-2823	Social-Demographic Aspects of Delayed Childbearing	145
1-2824	Research on Delayed Childbearing	146
1-2825	Research on Delayed Childbearing: The Determinants of Age at First Birth and Average Birth Interval	147
1-2826	Research on Delayed Childbearing	148
1-2827	A Dynamic Model of the Expectations and Fertility of Childless Women	149
2-1052	Childcare and Fertility Expectation, June 1982	150
2-1054	Puerto Rican Fertility Survey	151
2-1055	Computerization of Fertility Tables for Birth Cohorts by Color: United States, 1917-1980	152

NICHD Annual Report
October 1, 1981 through September 30, 1982
Office of the Director, Center for Research
for Mothers and Children

The Center for Research for Mothers and Children (CRMC) supports research and research training activities related to the special health problems of mothers and children in the biomedical, social and behavioral sciences. Specifically, the CRMC develops and supports basic and clinical research and research training in the biological and behavioral aspects of, and environmental influences upon, normal and high-risk pregnancy, embryonic development, fetal growth and maturation, nutritional requirements during pregnancy and infancy, labor and the birth process, postnatal adaptation and maintenance of homeostasis, disorders of infancy, and the effect of perinatal events upon subsequent growth and behavioral development. The goal is to minimize the risk of morbidity and mortality during the perinatal and infancy period of life and to prevent subsequent functional impairment.

The Center also supports studies concerned with the precursors of many adult diseases and disabilities, focusing on congenital defects and developmental immunology, nutrition, metabolism, and endocrinology. These studies extend through adolescence to maturity. The goal is to prevent chronic disabilities by understanding their genetic, nutritional, metabolic and immunologic antecedents.

The research program of the CRMC includes studies related to the learning process as well as cognitive, personality and social development. Support is given for research that attempts to reveal the nature of the general learning process and certain specific processes such as the acquisition of speech and language and learning to read.

Studies of specific learning disorders such as developmental dyslexia are also a major concern. Personality, attitude formation, and social development of young children are investigated by different scientists such as developmental and experimental psychologists, sociologists, anthropologists, and pediatricians.

In addition, the CRMC has primary responsibility within the National Institutes of Health for research and research training in the area of mental retardation. It meets this responsibility through support of a wide range of biological, behavioral, and social research directly concerned with determining the causes and appropriate procedures for the prevention and elimination of the problem. Funds are provided through all of the regular NIH research support mechanisms and through core support to 12 Mental Retardation Research Centers located throughout the country.

On September 23, 1981, Dr. Sumner J. Yaffe, formerly Professor of Pediatrics and Pharmacology at the University of Pennsylvania, became the Director of the CRMC. Dr. Merrill S. Read, who had served as the Acting Director, CRMC, resumed full-time responsibility for the CNED Branch.

Throughout this reporting period, Dr. James F. Kavanagh continued to serve as the Associate Director of the Center.

On December 14, 1981, Dr. Donald McNellis, formerly an Obstetric Consultant with the Office of Maternal and Child Health, Bureau of Community Health Services, HSA, joined the Pregnancy and Perinatology Section of the CNED Branch.

On June 27, 1982, Dr. David B. Gray, formerly Adjunct Associate Professor of Psychology, University of Minnesota, joined the Human Learning and Behavior Branch as a Health Scientist Administrator.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Clinical Nutrition and Early Development Branch
Center for Research for Mothers and Children

The CNED Branch is the largest Branch in the CRMC. Support is provided for both research and research training utilizing both grant and contract mechanisms. The CNED Branch contains the following three Sections:

Genetics and Teratology Section supports research into the underlying mechanisms controlling both normal and abnormal development, and is structured around the following areas: developmental genetics, developmental biology, teratology, and developmental immunology. Clinical as well as basic studies are emphasized. The goal of this program is to prevent, alleviate and treat birth defects with a special focus on the structural defects.

Pregnancy and Perinatology Section supports research to advance knowledge on pregnancy and maternal health, fetal growth and maturation, and newborn well-being. Program goals take into account the interrelationships of specific health and developmental problems occurring in the prenatal, perinatal and infant periods of life, and the effects these events may have on the development and well-being of the child. Activities are organized around five maternal-infant health problem areas: high-risk pregnancy, fetal pathophysiology, premature labor and birth, disorders of the newborn, and the sudden infant death syndrome.

Nutrition and Endocrinology Section supports research and research training on the roles played by nutrients and hormones in development during fetal life, infancy, childhood, and adolescence. Program goals include the achievement of a better understanding of the relationships between nutrient and hormonal factors during normal growth and development as well as in growth retardation and developmental disorders of the endocrine system.

Table 1 summarizes the grant and contract programs for each of the three CNED Sections, giving the dollars and numbers of projects active in June, 1981. Detailed reports of the accomplishments of each of the Sections are presented in the following pages.

During FY 82 a major research expansion was achieved concerning the composition and nutritional values of human milk, the maternal and environmental factors affecting milk composition, and the usefulness of human milk for improving health and development of premature or other high-risk infants. This expansion required coordinated use of both grants and contracts. A research workshop entitled "Breast Milk Banking-Current Status and Future Needs" was held to review achievements midway through this multi-year effort.

Highlights of Branch efforts also included organization of two other research workshops. These were directed towards areas of high programmatic relevance which were judged to be ready for the interdisciplinary push that could only come from an exchange of ideas among leaders active in divergent aspects of the given field. These workshops were: (1) Normal and Abnormal Limb Development; and (2) Physical Activity in Pregnancy. It is anticipated that these workshops will lead to program announcements to further expand our research portfolios.

The Branch participated in the NICHD-wide Program Announcement calling for more research on Adolescence. Of special concern are studies on adolescent pregnancy and the special nutritional needs of the adolescent.

The Branch was pleased to add an obstetrician, Dr. Donald McNellis, to the staff of the Pregnancy and Perinatology Section to provide leadership in research on high-risk pregnancy and the initiation of labor.

Table 1.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1982
CLINICAL NUTRITION AND EARLY DEVELOPMENT BRANCH

Health Area	Funds (thousands)													
	Total		Research Grants						RCP Awards		National Research Service Awards		Research Contracts	
	No.	Funds	Total Research		Research Projects		Program Projects		Awards		Funds		Funds	
			No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	722	\$72,459	631	\$64,857	540	\$52,046	34	\$10,651	57	\$2,159	66	\$3,999	25	\$3,603
Genetics and Teratology	273	25,512	241	23,295	206	20,569	4	1,534	31	1,192	32	2,217	-	-
Pregnancy and Perinatology	258	29,455	224	26,435	195	18,103	14	7,734	15	598	18	1,089	16	1,932
Nutrition and Endocrinology	191	17,491	166	15,127	139	13,374	16	1,384	11	370	16	693	9	1,671

Notes: 1) Excludes scientific evaluation grants.

2) The Genetics and Teratology Section excludes two contracts totaling \$159,903 funded from a source other than NICHD.

3) The Minority Biomedical Support grants (S06) are included with the research projects.

4) Subprojects of program projects are counted individually in the Clinical Nutrition and Endocrinology Section.

THE GENETICS AND TERATOLOGY SECTION

Three to seven per cent of children are afflicted with developmental defects at some time in their lives; for the great majority of these conditions the cause remains unknown. But with new technologies such as improved cell cultures, recombinant DNA, and monoclonal antibodies, basic biological and clinical studies can be better integrated to improve understanding of human developmental errors. New epidemiological models also allow more sophisticated data analysis.

Congenital defects represent a high priority research area within NICHD. They are broadly defined to include all the inborn structural, functional and biochemical defects found in the human organism which are initiated prior to birth or shortly thereafter, and which cause immediate or delayed abnormality. Structural defects are given special emphasis. Studies of both normal and abnormal limb development are identified as a highlighted research area for immediate attention.

Most congenital defects start during early development, perhaps as early as the egg or sperm with consequences for the embryo, fetus and child. The resulting developmental errors can be expressed as early death, spontaneous abortion, stillbirth, dysmorphology, growth disorders and/or post-natal developmental dysfunctions. The causes of congenital defects are multiple, but five etiologic categories are emphasized in this research program: gene mutations, chromosomal aberrations, environmental agents, multifactorial causes and those of unknown origin. It should be noted that some malformations may not be due to genetic or external environmental factors, but may represent intrinsic errors of embryonic development.

The Genetics and Teratology Section has been divided into four component research areas which complement each other, but which also contain some overlap so that the various activities must be viewed together as an overall effort. These areas comprise:

- (1) Developmental Genetics to determine the hereditary influences underlying developmental disorders and to understand hereditary instructions for the developmental process,
- (2) Developmental Biology to determine the mechanisms underlying normal human development against which aberrations of this process can be understood.
- (3) Teratology to assess adverse genetic and/or environmental influences on development, and to arrive at mechanisms by which developmental aberrations are produced, and
- (4) Developmental Immunology to understand maturation of the immune system as well as adverse pregnancy and early postnatal outcome produced as a consequence of immunologic responses or immaturity of the defense system.

In fiscal year 1981 the Genetics and Teratology Section funded a total of 248 projects at the level of \$22,666,000 (Table 1a). This included 17 Institutional National Research Service Awards and 9 Individual National Research Service Awards which represent \$1,985,000 or 8.8% of the total research funds for this Section.

DEVELOPMENTAL GENETICS

Research in developmental genetics includes family studies to determine inheritance patterns and genetic contributions to inherited disease, twin studies to help separate genetic from maternal and external environmental contributions to developmental problems, and population studies to establish distributions and frequencies of abnormal genes. Clinical studies of specific genetic diseases investigate the phenotypic changes in relation to gene abnormalities and biochemical malfunctions. Basic biological approaches seek to identify the specific gene involved in a normal or abnormal developmental process and to determine the gene structure, function, and regulatory mechanisms governing gene action. Also included is the "switching" on and off of genes at specified developmental stages. Other studies are concerned with assignment of normal and abnormal genes to specific chromosomes or chromosomal loci.

Progress in genetics research is exemplified by a group of NICHD-supported investigators who have turned harmless laboratory bacteria into "factories" for the production of insulin for human use in diabetes mellitus. Using both the chemical synthesis of DNA and recombinant DNA methods, insulin has been produced by incorporating a synthesized gene for insulin into bacteria. Production of insulin in this transformed bacteria is an example of basic research potentially capable of producing a marked impact on human disease states.

DEVELOPMENTAL BIOLOGY

Studies in developmental biology pursue a better understanding of the mechanisms underlying human development. Investigators attempt to learn how highly specialized tissues and organs form from a series of divisions of a single fertilized egg. One category of studies is concerned with early development of the embryo. These investigations are directed toward an understanding of the mechanisms whereby cells in particular regions of the young embryo become developmentally committed so that they can undergo final expression during maturation of specific organ systems at later developmental stages. Other studies are grouped into categories based on the tissue or organ under study: limb development, cartilage formation, muscle differentiation and central nervous system development.

Remarkable advances are being made in developmental biology by a group of investigators attempting to identify genetic and epigenetic mechanisms underlying normal and abnormal mammalian differentiation. Stem cells of a malignant mouse tumor (teratocarcinoma), when injected into a normal early mouse embryo at the blastocyst stage, are able to become integrated into the embryo, to lose their malignancy, and to participate in a stable and normal manner in full somatic as well as functional germ-cell differentiation. Mutant teratocarcinoma cell lines can also be made to contain defects found in human genetic disease. Using these mutagenized cell lines a Lesch-Nyhan mosaic animal has already been produced and is being studied. These animal models hold great promise for the future study of human genetic disease as well as of normal and abnormal development.

TERATOLOGY

Studies in teratology are directed to the causes of aberrant development resulting in congenital defects. A mutant gene or chromosomal aberration, an environmental chemical or physical factor, a maternal metabolic disease or in-

fection are all potential etiologic factors. Investigations focus on clinical medicine, biochemical and molecular genetics, cellular and molecular biology, epidemiology, reproductive biology, and developmental pharmacology and toxicology.

An interesting research advance for one group of congenital defects is the development of a test for use in cases of ambiguous genitalia in newborns. The test identifies a male factor, possibly no more than a single gene, which sometimes is attached to a chromosome other than the usual Y. This hidden "male" antigen has been called the H-Y antigen and may be the result of a mutation or an accidental transfer of genes between chromosomes. Further refinement of this test is now underway.

DEVELOPMENTAL IMMUNOLOGY

Studies in developmental immunology are closely related to studies of congenital defects. Five research categories are pursued. Studies of the ontogeny of immunity seek errors in maturation that lead to mild as well as severe immune deficiency states in man. Other investigations evaluate decreased immunologic competence associated with malnutrition in infants. An NICHD conference on Trace Element Regulation of Immunity and Infection was held in September 1981 and should provide the stimulus for new studies in nutritional immunology. The immunology of breast milk is being investigated since current studies suggest that ingestion of colostrum and milk may contribute protective anti-infectious components to the newborn. Another category includes studies of neonatal infections which focus on immaturity and developmental deficiencies in body defenses associated with specific types of organisms. Studies in reproductive immunology look for maternal-fetal immunologic mechanisms that protect the fetus from a potentially harmful maternal immunologic environment.

Recently an NICHD-supported investigator has shown that thymic hormone (thymosin) can enhance lymphocyte response in some patients with cellular immunodeficiency disease. Clinical trials with thymosin therapy are now being carried out. Patients currently receiving thymosin therapy who have exhibited improvement in immunologic function and clinical status include individuals with thymic hypoplasia and immunoglobulin synthesis, ataxia-telangiectasia, severe atopy and hyper IgE syndrome, and combined immunodeficiency and short-limbed dwarfism. When reviewed in its entirety, the Program of the Genetics and Teratology Section clearly demonstrates the importance of basic biochemical and molecular research in developing solutions to major clinical problems confronted in modern health care.

STAFF ACTIVITIES

Section staff participate in various trans-NIH activities and joint efforts with other government agencies. These include membership on the NIH Coordinating Committee For Blood-Related Activities and a new working group on Blood and Its Substitutes established by the Interagency Technical Committee On Heart, Blood Vessel, Lung and Blood Resources. A staff member has been appointed to the NIH Cystic Fibrosis Coordinating Committee which functions to stimulate and plan for research activities across NIH. An international cystic fibrosis conference was planned and jointly funded through this effort. Representation on the NIH Working Group For Reye Syndrome facilitates coordination of research efforts on this important problem. This Working Group has published an NIH

Announcement representing the research needs of five different Institutes or components within NIH. Similarly, the Work Group sponsored an NIH Consensus Development meeting on Reye Syndrome which was held in March 1981. Staff also participates in the planning committees of the Fogarty International Center for the development of two international conferences: (a) International Symposium on the Control of Measles; and (b) International Symposium on Increased Control of Poliomyelitis and the Feasibility of Eradication. A member of the Section has also been appointed to the Genetics Education Committee of the Health Services Administration (HSA). This committee is developing recommendations for the improvement of genetics education in the HSA-funded State Grant Programs providing genetic services across the nation. The second of two workshops on genetics education was developed by this committee and held in August 1981. As a direct result of the NICHD conference on Trace Element Regulation of Immunity and Infection, a "Nutritional Immunology Club" will begin to hold annual gatherings at the time of the meetings of the Federation of American Societies for Experimental Biology. This is expected to improve information exchange and foster collaborative research activities.

Table 1a.
 NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1982
 GENETICS AND TERATOLOGY SECTION

Health Area	Funds (thousands)														
	Total		Research Grants						RCP Awards		National Research Service Awards		Research Contracts		
	No.	Funds	Total Research	Research Projects	Program Projects	Research Projects	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.
Total	273	\$25,512	241	\$23,295	206	\$20,569	4	\$1,534	31	\$1,192	32	\$2,217	-	-	
Clinical Genetics	15	1,915	15	1,915	11	1,382	1	409	3	124	-	-	-	-	
Basic Developmental Genetics	48	4,733	44	4,623	30	3,334	2	835	12	455	4	110	-	-	
Developmental Biology, General	88	8,115	71	6,580	60	6,165	-	-	11	415	17	1,535	-	-	
CNS Development	13	990	12	973	12	973	-	-	-	-	1	17	-	-	
Limb Bud Development	6	348	5	329	4	289	-	-	1	40	1	19	-	-	
Chondrogenesis	7	1,027	7	1,027	7	1,027	-	-	-	-	-	-	-	-	
Myogenesis	13	1,141	12	1,124	11	1,084	-	-	1	40	1	17	-	-	
Teratology-Biological Causes	9	1,203	7	901	7	901	-	-	-	-	2	302	-	-	
Teratology-Physical & Chemical Causes	20	1,720	19	1,661	19	1,661	-	-	-	-	1	58	-	-	
Ontogeny of Immunity	17	1,448	15	1,380	12	1,012	1	290	2	79	2	67	-	-	
Neonatal Infection	14	872	12	800	11	760	-	-	1	40	2	72	-	-	
Immunology of Breast Milk	5	306	4	287	4	287	-	-	-	-	1	19	-	-	
Reproductive Immunology	18	1,693	18	1,693	18	1,693	-	-	-	-	-	-	-	-	

Notes: 1) Excludes scientific evaluation grant.
 2) The Minority Biomedical Support grants (S06) are included with the research projects.
 3) Excludes two research contracts funded from a source other than NICHD.

PREGNANCY AND PERINATOLOGY SECTION

The Pregnancy and Perinatology Section supports a program of research and research training to promote knowledge related to maternal health and pregnancy, fetal growth and maturation, and well-being of the newborn. Of special interest are maternal health problems that affect fetal and infant health, problems facing the newborn infant in adapting to extrauterine life, and events in the neonatal period that can influence the growth and development of the child.

RESEARCH ACTIVITIES

Activities of the Section are organized around five maternal-infant problem areas (Table 1b) which will be described in subsequent sections. The funds were divided among 258 research grants and contracts and amounted to \$29.4 million, approximately 26% of the holdings of the Center for Research for Mothers and Children. Research training support accounted for 3.7% of this amount.

High Risk Pregnancy

Research under this rubric addresses a variety of conditions complicating the normal gestation process. Over the last 20 years significant progress has occurred in maternal survival and well-being which has surpassed improvements in fetal outcome. Research efforts are directed towards the closure of this gap while continuing studies in both normal and abnormal pregnancies. Emphasis is placed on examining the roles of the cardiovascular, respiratory, endocrine and genitourinary systems in women during normal pregnancy and their contribution to and/or involvement in abnormal conditions throughout gestation. These conditions include toxemia, diabetes, hypertension, malnutrition, isoimmunization, viral and bacterial infections, blood dyscrasias, anemia, and hemorrhagic phenomena associated with pregnancy. Other research focuses on placental function; the maintenance of pregnancy; the impact of common pollutants, drugs and anesthetics on the mother and fetus; and the psychosocial dynamics of pregnancy. An area of developing interest will examine the effects of maternal exercise on her well-being and on the health of her offspring. Pregnant adolescents are a high-risk group for abnormal fetal outcome, and studies are encouraged to elucidate the biologic reasons for the recognized greater hazard, particularly among very young mothers.

Fetal Pathophysiology

Studies in fetal pathophysiology are examining the factors influencing normal and abnormal embryonic development. They seek a better understanding of events which interfere with the processes of growth and maturation in the fetus. Therefore efforts are focusing on normal and abnormal development at the molecular, tissue, and organ levels. Emphasis is placed on biochemical, genetic and biophysical studies for assessing fetal status that can provide meaningful antenatal diagnosis. In addition, attention is given to metabolic, nutritional, physiologic, pharmacologic, and immunologic factors involving the mother and her developing fetus. Studies addressing the effects of maternal exercise upon the fetus and its possible influence in producing fetal hypoxia are being encouraged.

Premature Labor and Birth

Premature labor and birth is a major cause of neonatal mortality and morbidity. Two-thirds of all infant mortality occurs among infants weighing 2500 grams or less at birth. Furthermore, the nation's high prematurity rate is responsible for our relatively poor performance in infant mortality compared to other countries. Consequently there is a great interest in studies of the normal onset of labor, why labor sometimes begins prematurely, how premature labor might be stopped without detrimental effects, and the mechanism(s) of intra-uterine growth retardation. These studies are addressing such topics as endocrine factors that maintain pregnancy and initiate labor, mechanisms responsible for labor dystocia and approaches for prevention and treatment. The Section is also interested in recognizing indicators of impending labor.

Disorders of the Newborn

Disorders of the newborn are responsible for approximately three-fourths of the infant deaths in the United States, and produce long term disability for many individuals who are affected by them and survive. Research directed toward reducing the impact of these disorders includes studies of maternal health problems that affect the status of the infant, adaptation of the newborn infant to its environment, and problems in the early weeks of life that influence subsequent development and behavior. Problems of particular importance are neonatal sepsis, intraventricular hemorrhage, respiratory distress syndrome, necrotizing enterocolitis, jaundice, and care of the low birthweight infant.

The Sudden Infant Death Syndrome

The sudden infant death syndrome (SIDS) was singled out for special research emphasis by Congress in 1974. The Institute has made particular efforts to encourage research on this problem, and as a result the program has had significant growth. A major consequence of this increased research has been a change in the basic concept of the SIDS infant, who is no longer viewed as having been perfectly healthy prior to death, but rather is believed to have had developmental abnormalities. This revised concept suggests that a profile of infants at particular risk for SIDS might be developed so that intervention and prevention efforts can be targeted to a high risk population. Current research efforts are directed toward specifying these risk factors, identifying the cause(s) of SIDS, and improving methods for helping families cope with a SIDS death.

MAJOR RESEARCH PROGRAMS (MRPs)

Major Research Programs (MRPs) have been established by the Institute to provide an integrated approach to major unresolved problems in perinatal medicine. These MRPs support multidisciplinary research in areas where knowledge gaps have not been sufficiently addressed by ongoing research, or where promising areas are in need of special stimulation. The Section supports the seven MRPs funded by the Institute; four are in the area of diabetic pregnancies, and one in each of the following subjects: prematurity, SIDS, and fetal hypoxia.

RESEARCH ACCOMPLISHMENTS OF MRPs

Four MRPs are in the area of "Diabetic Pregnancy," a major problem for mothers and children. Maternal morbidity is higher in diabetics and, although fetal

mortality in diabetic pregnancy has been reduced, it is not yet at the level in the general population. Congenital anomalies, macrosomia, late intrauterine death and RDS remain significant problems. Investigators in these MRPs are attempting to clarify the pathophysiology of maternal metabolic disorders causing changes in the intrauterine environment which are unfavorable for the developing fetus. An important aspect of the studies evaluates the question of whether infants of diabetic mothers incur a greater risk of impaired cognitive development. Evidence on this issue is conflicting. Fetal behavioral states are being recorded in the diabetic population and seem to match the less mature AGA (appropriate for gestational age) population at similar gestational ages. One aspect of maternal metabolism under examination is the effect of dietary deprivation. The parameters measured (glucose, alanine, insulin, glucagon, FFA and B hydroxybutyrate) were profoundly altered after an extension of overnight fast in pregnant subjects in contrast to non-pregnant women. These and other studies confirm that the criteria of metabolic normalcy based on observations in nongravid females cannot be used to assess fuel homeostasis in late pregnancy. Alterations in placental composition in rats with experimental diabetes show an increase in glycogen/DNA and triglycerides/DNA which has also been found in human placentas. The use of continuous insulin infusion in the mother did not cause deleterious effects and resulted in the normalization of maternal metabolism. The ultimate benefits of this type of intervention is currently being assessed; it appears that rigid regulation of maternal diabetes does normalize glucose production rate in her infant. Many other studies are being carried out which eventually will help in the understanding of the problems and the delineation of appropriate care for diabetic pregnancies.

Investigators of the MRP entitled "SIDS: Study of Etiology and Perinatal Risk Factors" have directed their efforts towards the identification of infants who have respiratory instability during feeding and during sleep in order to determine if specific abnormalities can be recorded. Although some preliminary findings suggest thyroid dysfunction in SIDS victims, this issue has raised many questions which are being pursued systematically.

The MRP dealing with fetal hypoxia addresses the question of maternal health problems associated with smoking and forms of fetal distress that may involve hypoxia leading to neurological deficit and/or intrauterine growth retardation. Studies on fetal hypoxia are performed with humans and parallel experimental observations are obtained in the baboon. Sixteen smoking patients enrolled in the program have delivered infants of lesser weight than their controls. A changing pattern of smoking during pregnancy suggests a decrease in the number of cigarettes smoked between 22-31 weeks of gestation with a return to slightly higher levels during the latter half of the third trimester. Carboxyhemoglobin levels at birth are higher in the fetus than in the mother. This finding is preliminary and laboratory data and procedures are being re-examined. The baboon is an appropriate experimental model for this study as the fetal breathing patterns and responses to glucose load in the mother are similar to those obtained in humans. The smoker's placentas have evidence of maternal vascular compromise and inflammation of the endometrium. In a rat model these investigators demonstrated that an increased exposure to cigarette smoke progressively decreases food intake. It seems that the adverse effects of heavy maternal smoking on the fetus are partly mediated through hypoxia and can be considered as a model of chronic intrauterine hypoxia. Fetal

growth retardation is also observed with chronic maternal hypertension; work in the MRP is also studying this group of patients.

There is clear precedent in gestational physiology for the various compartments (maternal, fetal, and placenta) to function cooperatively, for example for steroid hormone production. One Major Research Program is gathering evidence that there is a biochemical communication system involving gestational compartments that can set in motion events leading to human parturition. While it has been known for some time that prostaglandins cause physiologic uterine contractions, this program has identified the fatty precursor of prostaglandins, namely arachidonic acid, and has characterized its forms and enzymes necessary to release arachidonic acid from storage. Because steroid production by the placental-fetal compartment appears to be important in biochemical events associated with parturition, considerable effort has been expended to elucidate factors that may regulate steroid production. It has been determined that low-density lipoprotein (LDL) is the principal source of cholesterol used by the placenta for steroid hormone biosynthesis, and that, therefore, factors regulating LDL metabolism determine the steroidogenic capacity of the placenta. A unique metabolic pathway for the metabolism of progesterone has been found and appears to reside in the fetus. The exact role of this pathway, which does not exist in non-pregnant humans, remains to be clarified. Much of the work tends to implicate the fetal membranes as the metabolic focus of events leading to parturition. The membranes are significantly situated between amniotic fluid, which may receive biochemical signals from the fetus, and the myometrium, which has contractile capability. Thus, the amniotic fluid-membrane-decidual complex may eventually be shown to be the most important gestational compartment, from the standpoint of parturition.

RESEARCH ACCOMPLISHMENTS UNDER THE GRANTS PROGRAM

Selected scientific accomplishments during FY 82 pertinent to the Section's five problem areas are highlighted in the following paragraphs:

The concept of high-risk pregnancy has focused attention in recent years on the biomedical and social factors associated with poor pregnancy outcome, including fetal and neonatal mortality. One investigator reports that epidemiologic studies in the past have not separated fetal deaths that occur during labor (intrapartum) from those occurring before labor. He reasoned that the associations and preventability of intrapartum fetal mortality would probably be very different because of the dissimilar circumstances of the occurrence. Thus, he has begun such a differential analysis of the two categories of fetal death. This line of research will improve our understanding of the problem of perinatal mortality, and point to the risk factors associated with specific types of mortality, so that research can take appropriate directions.

Pregnancy-induced hypertension (PIH) or toxemia, remains one of the most common complications of pregnancy, affecting approximately 7% of gestations. In addition, this complication accounts for a large portion of maternal mortality and is associated with increased perinatal morbidity and mortality. The cause of PIH has eluded researchers for decades. One etiology involves utero-placental ischemia, and this possibility has been pursued by one investigator by partial uterine artery occlusion. This technique performed in baboons

before pregnancy resulted in a clinical syndrome that resembled human PIH, both clinically and pathologically. A further refinement of this primate model of PIH is being attempted by performing the occlusive procedure during early pregnancy. The first results suggest that the hypertensive syndrome can also be produced under these circumstances. If a reliable animal model for PIH can be produced, the etiologic mechanism can be researched and appropriate preventive and therapeutic approaches evaluated.

Over the last decade evidence has grown indicating that a number of hormones (including vasoactive mediators) play an important role both in fetal homeostasis and in the adaptation of the newborn to extrauterine life. The precise way in which these hormones interact to maintain fetal homeostasis is not well understood. Perinatal asphyxia has been implicated in adverse effects. A group of researchers are studying the function of the kidney, an organ which plays a vital role in the restoration of plasma composition following an hypoxemic insult. They are examining the effects of hypoxia on release of hormones and on renal function in the fetal lamb during the third trimester of intrauterine life and compare them to the effects on the newborn during the immediate postnatal period. Hypoxemia produced by administration of 10% oxygen in nitrogen results in a 50% reduction in PO_2 in the pregnant ewe, fetus or newborn but only minimal change in PH or blood pressure. A fall in urinary output, a decrease in glomerular filtration rate and an increase in urine osmolality occur in both fetus and newborn. This change in renal function accompanied by modifications in plasma levels of vasoactive substances indicate that hypoxia is an important stimulus in their production.

There are many possible avenues of research to examine the causes of preterm labor. One project consists of a multifaceted approach to examine endocrine, immune and infectious mechanisms in a prospective manner. Early results indicate that: (1) serum cortisol levels are low in many women who experience preterm labor, and that tocolytic therapy restored cortisol levels to the normal range; (2) an immunosuppressive factor associated with normal pregnancy is deficient in some cases of preterm labor; and (3) the organism chlamydia appears to be prevalent in the genital tracts of women who subsequently have preterm labor. Thus, a multi-factorial picture of causation of preterm labor appears to be emerging, indicating the importance of diagnosis and appropriate therapy in each individual case. Some researchers believe that preterm labor and birth may indicate a failure of the hormonal mechanisms that normally inhibit parturition until term. In fact, a sharp decline in the production of progesterone precedes parturition in most mammalian species, but has not been documented in humans. However, recent research suggests that local tissue concentrations of progesterone may be decreased without such reduction being detectable in peripheral circulation. Also, a hormonal mechanism has been identified in the fetus whereby the latter can reduce progesterone production in the placenta. Thus, better understanding of the role of progesterone in parturition may lead to opportunities to influence its concentration pharmaceutically, and therefore, perhaps inhibit premature labor.

Preterm labor and delivery remain major problems leading to perinatal morbidity and mortality. Drugs have been recently approved for the suppression of preterm labor, but side-effects and inapplicability to many clinical situations

has sustained the search for other approaches. The hormone oxytocin is thought to play a role in the uterine contraction process, and perhaps in the initiation of labor in some animals. One investigator has been studying the mechanisms by which drugs alter the storage and release of oxytocin from the posterior pituitary gland. Such studies may provide a basis for screening drugs with potential for inhibiting oxytocin release and therefore premature labor.

The serious nature of neonatal infection due to Group B streptococcus (GBS) disease continues to concern neonatologists. Rational approaches to the treatment and prevention must be based on basic knowledge of the natural course of maternal carriage of the organism during the prenatal period, and the epidemiology of the disease in terms of attack rate and the risk factors associated with neonatal disease. Early data suggest that vaginal colonization tends to be intermittent, so that antibiotic therapy before term is probably not indicated. Another important approach to this problem is immunologic. One investigator is measuring maternal serum antibodies to several specific GBS antigens and correlating them with susceptibility to infection in an animal model. Such studies could lead to clinical methods with which to predict neonatal susceptibility to GBS infection, and to evaluate the efficacy of GBS vaccines that are under development.

Respiratory distress syndrome continues to be an important problem during neonatal life. Studies are examining the biochemical pathways involved in the synthesis, storage, and secretion of disaturated phosphatidylcholine, the major component of pulmonary surfactant in the rat lung. They demonstrated that when fetal lung is isolated in an in-vitro system, it has considerable intrinsic potential for differentiation which suggests that important factors may originate in the lung. Indeed, specific active fractions have been isolated and are being purified and characterized.

Clinical entities such as apnea in early life and SIDS are being studied with the purpose of preventing their occurrence and determining appropriate treatment modalities. Investigators are examining the ways in which a developing animal controls ventilation and heart rate in response to stresses such as hypoxia in both REM and quiet sleep. These studies are determining if specific vulnerable periods exist and their possible relationship to sleep state. Preliminary results in puppies showed no differences in cardiac output in REM and quiet sleep suggesting that recorded differences in blood pressure are dependent on modifications in peripheral resistance. Measurements of catecholamines have helped in determining that newborns have much higher levels and brisker responses to hypoxia than adults. Studies are in progress to examine the role of endorphins in the maturation of ventilatory and cardiovascular functions during sleep under normoxic and hypoxic conditions.

RESEARCH TRAINING

Like other Branches and Sections of the NICHD, the CNPP Section has a firm commitment to support the postdoctoral research training of promising young investigators. In FY '82 the CNPP Section funded 11 Institutional National Research Service Awards (NRSA) in the area of perinatal medicine.

Conferences, Staff Activities, and Publications

During FY 1982, the Section provided partial support for the Perinatal Research Society's Annual Conference.

In September, 1982, the Section held a Research Planning Workshop on "Physical Activity in Pregnancy." The participants reviewed what is known about various effects on mother and fetus of exercise during pregnancy, to identify information that is needed, and to plan for future research. It is planned to publish a report from the workshop in a medical journal.

Staff members represented the Institute at a number of meetings of professional organizations, including the Society for Gynecologic Investigation, Society for Pediatric Research, and the American Pediatric Society.

Dr. Catz is the NICHD representative to the DHHS Committee to Coordinate Environmental and Related Programs (DHHS-CCERP). She also is a liaison representative of the NICHD to the Committee on Drugs of the American Academy of Pediatrics, and serves as an ex-officio member of the Maternal and Child Health Research Grants Review Committee of the Bureau of Community Health Services, Health Services Administration.

Publications by Section Staff include:

McNellis, D.: The Role of Antibiotics in the Management of Infections Associated with Pregnancy-Family and Community Health (In Press).

Sonawane, B.R., and Catz, C. Nutritional Status and Drug Metabolism during Development, In Soyka, L.F., and Redmond, G.P.: Drug Metabolism in the Immature Human, New York: Raven Press, 1981, p.p. 87-100.

Wald, N.J., Cuckle, H.S.; Catz, C.; Dayton, D., and Reimer, C.B.: Alpha Fetoprotein Screening and Diagnosis of Fetal Open Neural Tube Defects: The Need for Quality Control. Am. J. Obstet. Gynecol. 141: 1-4, 1981.

Table 1b.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1982
PREGNANCY AND PERINATOLOGY SECTION

Health Area	Total		Funds (thousands)										National Research Service Awards		Research Contracts	
	No.	Funds	Research Projects		Program Projects		RCP Awards		No.	Funds	No.	Funds	No.	Funds	No.	Funds
			No.	Funds	No.	Funds	No.	Funds								
Total	258	\$29,455	224	\$26,435	195	\$18,103	14	\$7,734	15	\$598	18	\$1,089	16	\$1,932		
High-Risk Pregnancy	78	9,419	67	8,134	60	5,289	5	2,768	2	77	4	246	7	1,038		
Fetal Pathophysiology	58	6,967	53	6,752	42	4,281	4	2,190	7	281	5	215	-	-		
Premature Labor and Birth	43	4,467	43	4,467	40	3,402	2	1,027	1	38	-	-	-	-		
Disorders of the Newborn	58	5,720	44	4,708	38	3,669	2	880	4	159	9	628	5	384		
Sudden Infant Death Syndrome	21	2,883	17	2,374	15	1,462	1	868	1	44	-	-	4	509		

Notes: 1) Excludes scientific evaluation grants.
2) The Minority Biomedical Support grants (S06) are included in with the research projects.

NICHD Annual Report
September 30, 1981 through September 30, 1982
Pregnancy and Perinatology Section
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Contract Number: N01 HD 9-2828

Contract Title: Non-human Primate Colony

Contractor: University of California, Davis, California

Money Allocated: \$224.371

Objectives: Under this contract, a colony of Rhesus monkeys (*Macaca mulatta*) of known medical, reproductive and genealogical history is being kept and developed at the California Primate Research Center, University of California at Davis. This colony serves as a resource of research animals of known quality from a standardized environment for investigators whose research is funded by the NICHD.

Procedures: Animals of different ages including dated pregnancies, embryonic and fetal material, neonates of known gestation, mother-infant pairs, juveniles of known age, as well as certain biopsy material, tissues, and fluids are being made available to selected investigators, all of whom must be directly determined by an advisory committee which also advises on colony and contract management. Animals are shipped to recipient scientists throughout the country; a limited number of investigators can also be accommodated to visit facilities on-site. Biological and behavioral data profiles are compiled and incorporated into the computerized record of each animal. This information is available to recipient investigators.

Significance: Demand for animals from this resource reflects the use of Rhesus monkeys as a model for the human in biomedical research.

Proposed Course: The size of the colony, stabilized at 335 animals is adequate for the projected demand of 8--100 pregnancies per year plus the need for replacement of breeder stock. A new RFP has been issued for competitive renewal of the Center contract, and the proposals received are undergoing review during the present fiscal year.

Project Officer: Charlotte Catz, M.D.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Pregnancy and Perinatology Section
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Contract Number: N01 HD 7-2840

Contract Title: Data Collection Center for the NICHD Cooperative Epidemiologic SIDS Risk Factors Study

Contractor: University of California
Davis, California

Money Allocated: No additional funding.

Objectives: This contract is an essential component of the NICHD Cooperative Epidemiologic SIDS Risk Factors Study involving one data coordinating center at the University of Washington (N01 HD 7-2839) and six data collecting centers (University of Washington, N01 HD 7-2839; University of California (Davis), N01 HD 7-2840; Health Research Inc., Albany, New York, N01 HD 7-2841; Medical and Health Research Association of New York City, N01 HD 7-2842; Loyola University (Chicago) N01 HD 7-2843; and St Louis Regional Maternal and Child Health Inc., N01 HD 7-2844.

The purpose of this study is the development of a risk prediction algorithm to be applied in the first week of life. The study design is case-control and population based. The sample consists of more than 800 possible SIDS cases and two matched living controls selected for each possible SIDS case.

Findings: Data collection began on October 9, 1978. Information was obtained through interviews with parents (usually mothers) of SIDS infants and of living infants matched with SIDS infants for age, birth weight, and race (Black/not Black). Pathology data (tissue specimens, gross autopsy, and death investigation reports) were obtained from coroners or medical examiners who performed autopsies on the SIDS infants. Entry of subjects into the study ended on December 31, 1979. Also obtained was a comprehensive set of data about the medical history of study infants and their mothers through abstraction of prenatal, delivery, and postnatal medical records.

Significance: The sudden infant death syndrome is the leading cause of death in the United States between one month and one year of life. This study is an integral part of the NICHD SIDS research contract program to understand the causes and underlying mechanisms of SIDS and to identify infants at risk.

Proposed Course: All interview data, including neighborhood and housing data on the interviewed families, and birth and death certificate data have been forwarded to the Data Coordinating Center. Pathology specimens and gross autopsy and death investigation reports have been sent to the Pathology Coordinating Laboratory for slide preparation and abstraction of information. Study Centers have participated in the development of data analysis strategies and in the presentation of results during FY 1982. A written report of the results from the initial analysis of the first 400 cases and their matched controls will be published in FY 1983.

Project Officer: Eileen G. Hasselmeyer, Ph.D.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Pregnancy and Perinatology Section
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Contract Number: N01 HD 7-2841

Contract Title: Data Collection Center for the NICHD Cooperative Epidemiologic SIDS Risk Factors Study

Contractor: Health Research, Inc.
Albany, New York

Money Allocated: No additional funding (December 1, 1981 - December 31, 1982).

Objectives: This contract is an essential component of the NICHD Cooperative Epidemiologic SIDS Risk Factors Study involving one data coordinating center at the University of Washington (N01 HD 7-2839) and six data collecting centers (University of Washington, N01 HD 7-2839; University of California (Davis), N01 HD 7-2840; Health Research Inc., Albany, New York, N01 HD 7-2841; Medical and Health Research Association of New York City, N01 HD 7-2842; Loyola University (Chicago) N01 HD 7-2843; and St Louis Regional Maternal and Child Health Inc., N01 HD 7-2844).

The purpose of this study is the development of a risk prediction algorithm to be applied in the first week of life. The study design is case-control and population based. The sample consists of more than 800 possible SIDS cases and two matched living controls selected for each possible SIDS case.

Findings: Data collection began on October 9, 1978. Information was obtained through interviews with parents (usually mothers) of SIDS infants and of living infants matched with SIDS infants for age, birth weight, and race (Black/not Black). Pathology data (tissue specimens, gross autopsy, and death investigation reports) were obtained from coroners or medical examiners who performed autopsies on the SIDS infants. Entry of subjects into the study ended on December 31, 1979. Also obtained was a comprehensive set of data about the medical history of study infants and their mothers through abstraction of prenatal, delivery, and postnatal medical records.

Significance: The sudden infant death syndrome is the leading cause of death in the United States between one month and one year of life. This study is an integral part of the NICHD SIDS research contract program to understand the causes and underlying mechanisms of SIDS and to identify infants at risk.

Proposed Course: All interview data, including neighborhood and housing data on the interviewed families, and birth and death certificate data have been forwarded to the Data Coordinating Center. Pathology specimens and gross autopsy and death investigation reports have been sent to the Pathology Coordinating Laboratory for slide preparation and abstraction of information. Study Centers have participated in the development of data analysis strategies and in the presentation of results during FY 1982. A written report of the results from the initial analysis of the first 400 cases and their matched controls will be published in FY 1983.

Project Officer: Eileen G. Hasselmeyer, Ph.D.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Pregnancy and Perinatology Section
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Contract Number: N01 HD 7-2839

Contract Title: Data Collection Center for the NICHD Cooperative Epidemiologic Study of SIDS Risk Factors

Contractor: University of Washington
Seattle, Washington

Money Allocated: No additional funding.

Objectives: This contract is an essential component of the NICHD Cooperative Epidemiologic SIDS Risk Factors Study involving one data coordinating center at the University of Washington (N01 HD 7-2839) and six data collecting centers (University of Washington, N01 HD 7-2839; University of California (Davis), N01 HD 7-2840; Health Research Inc., Albany, New York, N01 HD 7-2841; Medical and Health Research Association of New York City, N01 HD 7-2842; Loyola University (Chicago) N01 HD 7-2843; and St Louis Regional Maternal and Child Health Inc., N01 HD 7-2844.

The purpose of this study is the development of a risk prediction algorithm to be applied in the first week of life. The study design is case-control and population based. The sample consists of more than 800 possible SIDS cases and two matched living controls selected for each possible SIDS case.

Findings: Data collection began on October 9, 1978. Information was obtained through interviews with parents (usually mothers) of SIDS infants and of living infants matched with SIDS infants for age, birth weight, and race (Black/not Black). Pathology data (tissue specimens, gross autopsy, and death investigation reports) were obtained from coroners or medical examiners who performed autopsies on the SIDS infants. Entry of subjects into the study ended on December 31, 1979. Also obtained was a comprehensive set of data about the medical history of study infants and their mothers through abstraction of prenatal, delivery, and postnatal medical records.

Significance: The sudden infant death syndrome is the leading cause of death in the United States between one month and one year of life. This study is an integral part of the NICHD SIDS research contract program to understand the causes and underlying mechanisms of SIDS and to identify infants at risk.

Proposed Course: All interview data, including neighborhood and housing data on the interviewed families, and birth and death certificate data have been forwarded to the Data Coordinating Center. Pathology specimens and gross autopsy and death investigation reports have been sent to the Pathology Coordinating Laboratory for slide preparation and abstraction of information. Study Centers have participated in the development of data analysis strategies and in the presentation of results during FY 1982. A written report of the results from the initial analysis of the first 400 cases and their matched controls will be published in FY 1983.

Project Officer: Eileen G. Hasselmeyer, Ph.D.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Pregnancy and Perinatology Section
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Contract Number: N01 HD 7-2842

Contract Title: Data Collection Center for the NICHD Cooperative
Epidemiologic SIDS Risk Factors Study

Contractor: Medical and Health Research Association of New York City,
Inc. New York, New York

Money Allocated: No additional funding.

Objectives: This contract is an essential component of the NICHD Cooperative Epidemiologic SIDS Risk Factors Study involving one data coordinating center at the University of Washington (N01 HD 7-2839) and six data collecting centers (University of Washington, N01 HD 7-2839; University of California (Davis), N01 HD 7-2840; Health Research Inc., Albany, New York, N01 HD 7-2841; Medical and Health Research Association of New York City, N01 HD 7-2842; Loyola University (Chicago) N01 HD 7-2843; and St Louis Regional Maternal and Child Health Inc., N01 HD 7-2844.

The purpose of this study is the development of a risk prediction algorithm to be applied in the first week of life. The study design is case-control and population based. The sample consists of more than 800 possible SIDS cases and two matched living controls selected for each possible SIDS case.

Findings: Data collection began on October 9, 1978. Information was obtained through interviews with parents (usually mothers) of SIDS infants and of living infants matched with SIDS infants for age, birth weight, and race (Black/not Black). Pathology data (tissue specimens, gross autopsy, and death investigation reports) were obtained from coroners or medical examiners who performed autopsies on the SIDS infants. Entry of subjects into the study ended on December 31, 1979. Also obtained was a comprehensive set of data about the medical history of study infants and their mothers through abstraction of prenatal, delivery, and postnatal medical records.

Significance: The sudden infant death syndrome is the leading cause of death in the United States between one month and one year of life. This study is an integral part of the NICHD SIDS research contract program to understand the causes and underlying mechanisms of SIDS and to identify infants at risk.

Proposed Course: All interview data, including neighborhood and housing data on the interviewed families, and birth and death certificate data have been forwarded to the Data Coordinating Center. Pathology specimens and gross autopsy and death investigation reports have been sent to the Pathology Coordinating Laboratory for slide preparation and abstraction of information. Study Centers have participated in the development of data analysis strategies and in the presentation of results during FY 1982. A written report of the results from the initial analysis of the first 400 cases and their matched controls will be published in FY 1983.

Project Officer: Eileen G. Hasselmeyer, Ph.D.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Pregnancy and Perinatology Section
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Contract Number: N01 HD 7-2843

Contract Title: Data Collection Center for the NICHD Cooperative
Epidemiologic SIDS Risk Factors Study

Contractor: Loyola University of Chicago
Chicago, Illinois

Money Allocated: No additional funding (December 1, 1981 - August 31, 1982).

Objectives: This contract is an essential component of the NICHD Cooperative Epidemiologic SIDS Risk Factors Study involving one data coordinating center at the University of Washington (N01 HD 7-2839) and six data collecting centers (University of Washington, N01 HD 7-2839; University of California (Davis), N01 HD 7-2840; Health Research Inc., Albany, New York, N01 HD 7-2841; Medical and Health Research Association of New York City, N01 HD 7-2842; Loyola University (Chicago) N01 HD 7-2843; and St Louis Regional Maternal and Child Health Inc., N01 HD 7-2844).

The purpose of this study is the development of a risk prediction algorithm to be applied in the first week of life. The study design is case-control and population based. The sample consists of more than 800 possible SIDS cases and two matched living controls selected for each possible SIDS case.

Findings: Data collection began on October 9, 1978. Information was obtained through interviews with parents (usually mothers) of SIDS infants and of living infants matched with SIDS infants for age, birth weight, and race (Black/not Black). Pathology data (tissue specimens, gross autopsy, and death investigation reports) were obtained from coroners or medical examiners who performed autopsies on the SIDS infants. Entry of subjects into the study ended on December 31, 1979. Also obtained was a comprehensive set of data about the medical history of study infants and their mothers through abstraction of prenatal, delivery, and postnatal medical records.

Significance: The sudden infant death syndrome is the leading cause of death in the United States between one month and one year of life. This study is an integral part of the NICHD SIDS research contract program to understand the causes and underlying mechanisms of SIDS and to identify infants at risk.

Proposed Course: All interview data, including neighborhood and housing data on the interviewed families, and birth and death certificate data have been forwarded to the Data Coordinating Center. Pathology specimens and gross autopsy and death investigation reports have been sent to the Pathology Coordinating Laboratory for slide preparation and abstraction of information. Study Centers have participated in the development of data analysis strategies and in the presentation of results during FY 1982. A written report of the results from the initial analysis of the first 400 cases and their matched controls will be published in FY 1983.

Project Officer: Eileen G. Hasselmeyer, Ph.D.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Pregnancy and Perinatology Section
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Contract Number: N01 HD 7-2844.

Contract Title: Data Collection Center for the NICHD Cooperative
Epidemiologic SIDS Risk Factors Study

Contractor: St. Louis Regional Maternal and Child Health Inc.,
St. Louis, Missouri

Money Allocated: No additional funding.

Objectives: This contract is an essential component of the NICHD Cooperative Epidemiologic SIDS Risk Factors Study involving one data coordinating center at the University of Washington (N01 HD 7-2839) and six data collecting centers (University of Washington, N01 HD 7-2839; University of California (Davis), N01 HD 7-2840; Health Research Inc., Albany, New York, N01 HD 7-2841; Medical and Health Research Association of New York City, N01 HD 7-2842; Loyola University (Chicago) N01 HD 7-2843; and St Louis Regional Maternal and Child Health Inc., N01 HD 7-2844.

The purpose of this study is the development of a risk prediction algorithm to be applied in the first week of life. The study design is case-control and population based. The sample consists of more than 800 possible SIDS cases and two matched living controls selected for each possible SIDS case.

Findings: Data collection began on October 9, 1978. Information was obtained through interviews with parents (usually mothers) of SIDS infants and of living infants matched with SIDS infants for age, birth weight, and race (Black/not Black). Pathology data (tissue specimens, gross autopsy, and death investigation reports) were obtained from coroners or medical examiners who performed autopsies on the SIDS infants. Entry of subjects into the study ended on December 31, 1979. Also obtained was a comprehensive set of data about the medical history of study infants and their mothers through abstraction of prenatal, delivery, and postnatal medical records.

Significance: The sudden infant death syndrome is the leading cause of death in the United States between one month and one year of life. This study is an integral part of the NICHD SIDS research contract program to understand the causes and underlying mechanisms of SIDS and to identify infants at risk.

Proposed Course: All interview data, including neighborhood and housing data on the interviewed families, and birth and death certificate data have been forwarded to the Data Coordinating Center. Pathology specimens and gross autopsy and death investigation reports have been sent to the Pathology Coordinating Laboratory for slide preparation and abstraction of information. Study Centers have participated in the development of data analysis strategies and in the presentation of results during FY 1982. A written report of the results from the initial analysis of the first 400 cases and their matched controls will be published in FY 1983.

Project Officer: Eileen G. Hasselmeyer, Ph.D.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Pregnancy and Perinatology Section
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Contract Number: N01 HD 8-2845

Contract Title: Pathology Coordinating Laboratory (PCL) for the NICHD
Cooperative Epidemiologic Study of SIDS Risk Factors

Contractor: Office of Medical Examiner
City and County of San Francisco
San Francisco, California

Money Allocated: \$34,165 (January 1, 1982 through December 31, 1982)

Objectives: This contract serves as the Pathology Coordinating Laboratory to the NICHD Cooperative Epidemiologic Study of SIDS Risk Factors. The Laboratory provides essential pathological services to enable the histological review of autopsy material by the Pathology Study Panel. The necropsy, a common gross dissection protocol, was followed by participating coroners and medical examiners. The contractor processed tissues submitted by the six Study Centers, and produced a set of uniformed slides for each infant entered into the study.

Findings: A common gross dissection protocol was developed. Medical Examiners and Coroners serving the six Study Centers followed the protocol during the period of data collection (October 9, 1978 - December 31, 1979). The PCL has received tissues from 941 infants who have died. Of these deaths, more than 800 have been designated SIDS cases; the balance includes quality control cases and some cases where subsequent diagnosis elicited a cause of death. The initial review of all slides by the Pathology Study Panel has been completed. Abstraction of Death Investigation Reports and Autopsy Reports were completed during FY 1982.

Significance: The sudden infant death syndrome is the leading cause of death in the United States between one month and one year of life. This study is an integral part of the NICHD SIDS research contract program to understand the causes and underlying mechanisms of the sudden infant death syndrome and to identify infants at risk.

Proposed Course: It is planned that the Pathology Study Panel will perform a review of all case material to determine the certainty with which they would classify a case "SIDS". The Pathology Coordinating Laboratory will coordinate this effort and abstract the results for entry onto the SIDS data tape located at the Data Coordinating Center. The PCL will continue to provide assistance to the Data Coordinating Center in the editing of the pathology data and in developing a system for cataloguing the pathology material for use as a research source.

Project Officer: Eileen G. Hasselmeyer, Ph.D.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Pregnancy and Perinatology Section
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Contract Number: N01 HD 7-2839

Contract Title: Data Coordinating Center for the NICHD Cooperative
Epidemiologic Study of SIDS Risk Factors

Contractor: University of Washington
Seattle, Washington

Money Allocated: \$317,340 (January 1, 1982 - December 31, 1982)

Objectives: This contract serves as the Data Coordinating Center to the NICHD Cooperative Epidemiologic SIDS Risk Factors Study. It is responsible for the processing, management, and analyses of data collected by the participating Study Centers.

Findings: During the current fiscal year, the Data Coordinating Center has continued to clean and edit the interview data. These data include, in addition to interview schedule data, data on the neighborhood and housing of interviewed families and birth and death certificate data. Pathology data from the necropsy checklist, microscopic examination report, and gross autopsy and death investigation reports from the participating coroners and medical examiners are being entered as they become available. Three files have been established to receive and store the data from this study.

Significance: The sudden infant death syndrome is the leading cause of death in the United States between one month and one year of life. This study is an integral part of the NICHD SIDS research contract program to understand the causes and underlying mechanisms of the sudden infant death syndrome and to identify infants at risk.

Proposed Course: Cleaning and editing of data by the Data Coordinating Center should be completed by February, 1983. Development of strategies for data analysis began in late 1979, and have continued through the current fiscal year. The data obtained regarding the first 400 cases and their 800 matched controls will be used to examine currently existing hypotheses of SIDS etiology, and to identify refined hypotheses through exploratory analysis on the first half of the data set. Results of the first descriptive analyses of the data set were reported in FY 1982. Further presentations are planned for FY 1983. A written report of the results from the initial analysis of the first 400 cases and their matched controls will be published in FY 1983.

Project Officer: Eileen G. Hasselmeyer, Ph.D.

NUTRITION AND ENDOCRINOLOGY SECTION

The Nutrition and Endocrinology Section supports research and research training on developmental aspects of nutrition, endocrinology, physiology, and physical growth. As of June, 1982, the Section supported 191 projects at a level of \$17,491,000. These projects are analyzed according to programmatic mechanism in Table 1c. Two-thirds of the total budget supported nutrition-related research, one-quarter supported endocrine-related research, and the remainder supported research on physiology and physical growth.

NUTRITION RESEARCH SUPPORT

Infant Nutrition

The Section's largest program is that of infant nutrition. Research interests include the nutrient requirements of normal, premature, and growth-retarded infants, as well as analysis of human milk, cow's milk, and synthetic formulas in relation to optimal infant development.

The biochemical immaturity of premature infants presents challenging problems that must be solved in order to design appropriate feedings for their enteral and parenteral nutrition. Investigators supported by the Section are currently working to develop nutrient mixtures that best meet the metabolic requirements of premature infants but do not violate their delicate mineral, acid-base, glycemic and osmolar balances.

Studies on human milk and milk banking comprise a large part of the infant nutrition program. Recently, scientists supported by the Section have discovered digestive enzymes, growth factors and immunocompetent B and T cells in human milk. Research is addressing the problem of how best to preserve the biological functions of these cells and proteins in the process of collecting and storing human milk and colostrum.

In June, 1981, the Section sponsored a workshop entitled "Determinants of Choice and Duration of Infant Feeding Practices" to consider hypotheses that relate various biomedical and socio-cultural variables to the choice of breast- or bottle-feeding and to the duration of breast-feeding. The proceedings of the workshop are now being edited for publication. In September, 1982, the Section scheduled a workshop entitled "Human Milk Banking: Current Status and Future Needs for Research". This workshop focused on both research and practical aspects of organizing and operating milk banks that can serve neonatal intensive care facilities.

Childhood and Developmental Nutrition

The Section supports research that emphasizes the roles played by various nutrients in cerebral and somatic development. These studies are designed to ascertain the effects, or lack of effects, of general and specific kinds of undernutrition on physical growth and cognitive development during infancy and childhood. For example, a project in Guatemala concerns the functional impact of iron deficiency anemia in infancy. Data from this study show that the Mental Development Index and the Psychomotor Development Index of the anemic

group were significantly lower than those of the non-anemic group. The more severe the iron deficiency, the greater the deficit. The most marked deficit was noted in 19-24 month-old infants.

Current world food policies are based on the assumption that if most of the energy needs of humans are satisfied by common staple foods, protein requirements will also be met. It has recently been learned that this assumption does not apply during late infancy and early childhood. Bulkiness of vegetable foods limits the amounts that can be consumed; poor digestibility may also limit the amount of utilizable protein available from such diets. Studies are underway in Peru to determine limits to consumption and digestion of wheat, oats, sorghum, and potatoes and their ability to satisfy protein needs. So far it has been learned that digestibility of wheat flour is excellent, although its lysine content is limited. Whole grain sorghum flour is poorly digested; it may contain an anti-nutritional factor, so that it should not be used as human food. Oats were found to have a high content of protein with excellent biological value. Results of this study should have an impact on world food policies and nutritional programs in developing countries since most of the world's weaned infants and children depend on vegetable protein diets.

Maternal-Fetal Nutrition

One of the most important of the Section's programs, especially from a preventive point of view, is that of maternal-fetal nutrition. This research explores the complex nutritional relationship that exists between the mother and her fetus. Exciting advances are now being made in nutritional therapy during fetal life of certain inborn errors of metabolism. Recently investigators supported by the Section successfully treated a fetus with biotin-responsive multiple carboxylase deficiency by providing its mother with oral biotin during pregnancy. Two affected siblings died who were not treated in utero. This kind of prenatal therapy has been successfully accomplished in only one other inborn error of metabolism, that of methylmalonic acidemia treated with vitamin B₁₂.

A major unsolved problem in the area of maternal-fetal nutrition is that of intrauterine growth retardation (IUGR). The etiology of IUGR, which affects approximately 100,000 pregnancies per year in this country alone, appears to be multifactorial in nature, involving not only maternal nutritional and endocrine status, but also placental circulation, maternal smoking, and maternal socio-economic status. An ovine model of IUGR is now being exploited to assess the feasibility of intrauterine nutritional therapy delivered directly to the fetus. Results show that fetal intragastric infusion of a solution of 4% glucose and 6.8% essential and non-essential amino acids significantly increases birth weight and crown-rump length when compared to unsupplemented fetuses of nutritionally deprived ewes. This discovery may pave the way for testing intrauterine nutritional therapy in humans.

Developmental Gastroenterology

This program area supports basic research on gastrointestinal development as well as clinical research on disorders such as celiac disease, lactase and other disaccharidase deficiencies, infantile diarrhea, necrotizing enterocolitis and food hypersensitivity. Nutritionally-oriented studies are of special interest because they relate to both the etiology and the therapy of gastrointestinal disorders.

Dietary treatment of obesity generally has been unsuccessful. This failure may be due to treating the symptoms rather than the cause of obesity. Scientists are now investigating the hypothesis that hypothalamic-pituitary dysfunction causes decreased thermogenesis and/or increased food intake. Studies of the hypothalamic-pituitary axis in obese Zucker rats (fa/fa) have shown that growth hormone plays a critical role in the development of obesity in this genetic model. Abnormal release of growth hormone leads to greater fat deposition. Other studies show that Zucker rats become obese even when their food intake is restricted to equal that of their lean littermates. These observations indicate that altered energy metabolism rather than increased dietary intake leads to excessive fat storage in this model. These and related observations suggest that the genetically obese rat is metabolically more efficient than non-obese rats and hence is able to store greater amounts of nutrients per unit of energy intake.

In FY 82 staff worked with the NIH Nutrition Coordinating Committee and the DHHS Nutrition Coordinating Committee in organizing a workshop on conceptual and methodologic issues in the definition and measurement of obesity in the American population. The proceedings of the workshop are now being edited for publication.

Nutritional Status

Research in this program area emphasizes the development of new methods for assessing nutritional status in pregnancy, infancy, childhood, and adolescence. Of special interest are methods which are noninvasive and pose the least possible risk to the individual while being precise, economical, and convenient. One example is the analysis of exhaled hydrogen, carbon dioxide and methane as a measure of adequacy of absorption in neonates. Another is the development of an oscillating air-displacement volumeter for measuring exactly small changes in the volume of infants fed various diets.

Adolescent Nutrition

The Section's program of adolescent nutrition emphasizes research in the areas of nutrient requirements during the adolescent growth spurt, obesity in adolescence, and nutrition of the pregnant adolescent. Stable isotope studies of hypocaloric dietary therapy for obese adolescents are in progress. Preliminary findings indicate that low-calorie diets containing protein and carbohydrate maintain nitrogen balance and spare lean body mass much better than do isocaloric diets of protein and fat. Data from this project also show that obesity during adolescence, even morbid obesity, is accompanied by significant increments in lean body mass.

Research on diet, life-style, and gain in lean body mass during pregnancy has disclosed that pregnant adolescents frequently have unhealthy life-styles characterized by smoking, alcohol consumption, and dietary inadequacies, including low intakes of protein, folate and vitamin C coupled with excessively high caloric intakes.

ENDOCRINE RESEARCH SUPPORT

The field of developmental endocrinology encompasses studies of hormonal influence on growth and development, studies of growth factors, and studies of the development of the hypothalamic-pituitary axis in relation to the thyroid, adrenal glands, and gonads.

Puberty

Much of this research explores the neurohumoral mechanisms involved in the control of the onset of puberty. Investigators supported by the Section have shown that pubertal onset is mediated by neurons which secrete luteinizing hormone releasing hormone (LHRH) and which are located in the medial basal hypothalamus in the region of the arcuate nucleus. These neurons appear to function as neuroendocrine transducers, releasing pulses of LHRH in a rhythmic manner at the onset of puberty.

An important observation in regard to the awakening of the pulsatile LHRH neurosecretory mechanism at puberty is that it actually represents a re-awakening. During fetal life the neurosecretory hypothalamus exhibits an unregulated pulsatile discharge of LHRH. During infancy and childhood, this pulsatile discharge is suppressed. Recent studies indicate that this suppression operates at two levels: an intrinsic inhibitory mechanism within the central nervous system, and a highly sensitive sex steroid negative feedback mechanism located within the gonadotropes of the pituitary gland.

By gaining a better understanding of the central origins of puberty, clinical investigators will be able to provide more effective therapy for the neuroendocrine disorders of precocious puberty and pubertal delay. The Section is currently funding clinical research on the use of a synthetic LHRH analogue (a decapeptide), in the treatment of precocious puberty. Initial therapeutic results have been most encouraging.

Growth Factors

An important facet of developmental endocrinology concerns the study of growth factors. The Section currently supports research on epidermal growth factor (EGF), nerve growth factor, somatomedins A and C, mammary stimulating factor, and human growth hormone (hGH). The definitive biological chemical research on EGF, including analysis of its amino acid sequence, has been supported by the Section. For instance, it has been shown that the EGF-receptor complex is closely associated with a tyrosine-specific protein kinase. This discovery has implications for understanding the cause of uncontrolled cell proliferation in tumors, because transformation of cells by several RNA tumor viruses seems to be mediated by virally-coded protein kinases which also phosphorylate tyrosine.

Recently, other investigators have learned that the amino acid sequence of somatomedin A is identical to that of insulin-like growth factor II and that the amino acid sequence of somatomedin C is identical to that of insulin-like growth factor I. Ultimately, pure somatomedins may be used as a specific therapy for Laron dwarves who respond to neither endogenous nor exogenous hGH.

Congenital Adrenal Hyperplasia

NICHD-supported investigators have been working to characterize further the clinical, genetic, and biochemical aspects of 21-hydroxylase deficient congenital adrenal hyperplasia (CAH). The discovery of linkage between the genes of the HLA locus and 21-hydroxylase made it possible in affected families to predict which siblings are carriers and which siblings are genetically unaffected. Recently it has been found that heterozygotes have a higher 17-hydroxyprogesterone response to stimulation by adrenocorticotrophic hormone (ACTH) than do genetically unaffected individuals.

HLA studies of families with classical 21-hydroxylase deficiency have led to the discovery of a cryptic form of the disorder, characterized by the presence of hormonal abnormalities without virilization, abnormal puberty, short stature or infertility. Another form of 21-hydroxylase-deficient CAH has been described in which the age of onset varies from five months to early adolescence. This type is called late onset CAH. Further studies of genetic markers for various forms of this disorder are underway.

DEVELOPMENTAL PHYSIOLOGY RESEARCH SUPPORT

This program is concerned with the development of physiologic feedback pathways by which homeostasis is achieved in blood volume, blood pressure and electrolyte balance. Investigators have shown that infants have lower glomerular filtration rates than adults and do not conserve some amino acids such as histidine and glycine as efficiently. Their low tubular transport capacity makes them vulnerable to the stresses of dehydration, electrolyte depletion, and acidosis during acute illness. Studies of the developing rabbit kidney have disclosed low levels of fluid and bicarbonate absorption during the first month of extrauterine life, followed by marked rises in absorption rates during weaning. Studies of the effects of early weaning and of various hormonal components of milk on kidney development are now underway.

PHYSICAL GROWTH RESEARCH SUPPORT

In this research area the Section is funding the development of new methods of mathematical descriptions of growth. These methods, which rely on computer-modeling, are expected to aid in interpretation of growth data and to make predictions of future growth in three dimensions, e.g., in craniofacial growth.

Work is also continuing on the development of an improved method for the measurement of skeletal maturity by radiologic analysis of knee, hand, and wrist growth. This research will aid in managing children who are receiving drugs or hormones that affect skeletal growth as well as those with unusual or asymmetric stature.

RESEARCH TRAINING IN NUTRITION AND ENDOCRINOLOGY

In FY 82 the Section continued to fund five Institutional National Research Service Awards (NRSAs) and initiated support of one new Institutional NRSA in pediatric endocrinology.

One of the Institutional NRSAs is devoted to developmental aspects of nutrition. This project currently has seven trainees enrolled at the post-doctoral level. These fellows are pursuing research projects that emphasize developmental aspects of clinical nutrition in prematurely-born babies and babies born at term. Of special interest are amino acid and essential fatty acid requirements of low birthweight infants. The other five Institutional NRSAs are concerned with developmental aspects of endocrinology and physiology. The seventeen post-doctoral fellows supported by these awards are working on projects that vary from studies of mechanisms of gonadotropin release to opiate receptor function.

In the area of developmental nutrition the Section currently funds four Individual NRSAs. The Section also funds eight Individual NRSAs in developmental endocrinology.

LIAISON ACTIVITIES

The professional staff of the Section represents the NICHD on a number of groups and committees in both the public and private sectors.

Section staff serve as the NICHD Representative to the NIH Nutrition Coordinating Committee. Dr. Grave also represents the Institute on the NIH Diabetes Mellitus Coordinating Committee as well as at Interagency meetings of the National Diabetes Advisory Board. In FY 82 Dr. Grave was detailed for two months to work on the Departmental Task Force on Assessment of the Scientific Evidence Relating to Problems of Infant Feeding.

Dr. Fjellstedt represents the NICHD on the NIH Digestive Diseases Coordinating Committee and also on the U.S.-Japan Cooperative Biomedical Sciences Panel on Malnutrition. Dr. Fjellstedt serves as NICHD liaison representative to the Committee on Nutrition of the Mother and Preschool Child of the Food and Nutrition Board of the National Academy of Sciences. He also serves as liaison representative to the Committee on Nutrition of the American Academy of Pediatrics.

Dr. Fjellstedt acts as the NICHD designated representative to the Board of Scientific Counselors of the USDA-Children's Nutrition Research Center in Houston, Texas.

Table 1c.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1982
NUTRITION AND ENDOCRINOLOGY SECTION

Health Area	Funds (thousands)													
	Total		Research Grants						RCP Awards		National Research Service Awards		Research Contracts	
			No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
	No.	Funds												
Total	191	\$17,491	166	\$15,127	139	\$13,374	16	\$1,384	11	\$370	16	\$693	9	\$1,671
Infant Nutrition	47	4,873	41	3,761	25	2,377	16	1,384	-	-	-	-	6	1,112
Childhood & Developmental Nutrition	15	1,427	13	1,241	13	1,241	-	-	-	-	2	186	-	-
Maternal-Fetal Nutrition	8	748	8	748	8	748	-	-	-	-	-	-	-	-
Developmental Gastroenterology	17	1,354	15	1,310	15	1,310	-	-	-	-	2	44	-	-
Cultural & Behavioral Aspects of Nutrition	13	1,357	11	893	11	893	-	-	-	-	-	-	2	464
Obesity & Childhood Antecedents of Adult Disease	12	1,256	12	1,256	9	1,142	-	-	3	114	-	-	-	-
Nutritional Status	2	104	2	104	1	63	-	-	1	41	-	-	-	-
Adolescent Nutrition	5	260	5	260	3	194	-	-	2	66	-	-	-	-
Developmental Endocrinology	57	4,661	47	4,317	44	4,206	-	-	3	112	9	249	1	95
Developmental Physiology	11	814	8	600	6	563	-	-	2	37	3	214	-	-
Physical Growth	4	637	4	637	4	637	-	-	-	-	-	-	-	-

Notes: 1) Excludes scientific evaluation grants.

2) Subprojects of program projects are counted individually.

3) The Minority Biomedical Support grants (S06) are included with the research projects.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Section on Nutrition and Endocrinology
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Name of Contractor: UNIVERSITY OF COLORADO
Denver, Colorado
Margaret C. Neville, Ph.D. - Principal Investigator
Contract No.: N01-HD-2-2801
Title: Human Milk Banking Studies
Date Contract Initiated: February 2, 1982
Current Annual Level: FY 82; \$179,787

Project Aims: This project will establish a set of reference values for selected constituents of breast milk at different stages of lactation and examine the effect of various maternal variables on milk composition, such as prematurity, adolescence, late lactation, concurrent pregnancy and lactation, induced lactation, drug therapy, special dietary idiosyncrasies, and chronic maternal disease. For the purposes of data control, levels of micronutrients and certain trace elements will be determined in colostrum and milk from a reference population of breast feeding mothers of full-term infants. Samples collected during these studies will be used to establish a repository of about 3,000 specimens which will be made available to other investigators for future studies on components which were not included in this study. An extensive compositional profile will be obtained on milk samples from these groups at numerous times during lactation. The concentrations of sodium, phosphorous, hydrogen ion, chloride ion, magnesium, calcium, phosphorus, total protein, non-protein nitrogen, lactose, total lipid, zinc, manganese, chromium, and copper will be monitored. Additional data such as amino acid profiles and measurements of free and protein bound calcium will be obtained on selected samples. Plasma levels on some of these substances will also be measured in order to attempt correlation with dietary and nutritional information that will also be recorded.

Significance to Biomedical Research and the Programs of the Institute: This project is one of a series of contracts examining various aspects of human milk. This project is unique in that it will be focusing on the maternal variables that contribute to variation in the composition of human milk.

Proposed Course: The project is in the beginning of the first year of three years of support. Funding in FY 83 is anticipated to be \$216,628 and for FY 84 \$233,999.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Section on Nutrition and Endocrinology
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Name of Contractor: YALE UNIVERSITY SCHOOL OF MEDICINE
New Haven, Connecticut
Richard A. Ehrenkranz, M.D. - Principal Investigator
Contract No.: N01-HD-2-2802
Title: Human Milk Banking Studies
Date Contract Initiated: February 1, 1982
Current Annual Level: FY 82; \$127,039

Project Aims: This new project has three major components:

- 1) The identification of mothers who successfully breast feed their pre-term infants, and the assessment of intervention to encourage breast feeding of the pre-term. Data will be collected that is designed to identify maternal factors such as smoking, alcohol intake, diet, experience, knowledge and attitudes which may affect the initiation or maintenance of breast feeding. The data obtained under this assessment study will be used to design this intervention study to be carried out later.
- 2) The determination of composition of pre-term milk as a function of length of gestation, of antenatal maternal intake of dexamethasone and/or beta-adrenergic drugs, of the duration of lactation, and of maternal stress. Daily milk volumes will be recorded, samples of milk representative of 24-hour periods will be collected on specific post-partum days and analyzed for total protein, the percent of whey and casein fraction, total nitrogen and non-protein nitrogen, immunoglobulins, lipids, lactose, sodium, potassium, chloride, calcium, phosphorous, water and energy.
- 3) The determination of immunologic properties of pre-term breast milk as a function of gestational age and of the drugs referenced under item number 2. Immunologic studies will be performed on breast milk samples taken at various days post-partum from mothers in each of three gestational age strata. Groups will include mothers who receive either dexamethasone, or ritodrine or both medications.

Significance to Biomedical Research and the Program of the Institute: This project will analyze human milk in ways that take into account the most likely clinical experience of mothers who are likely to deliver pre-term infants. Data on the milk of mothers in this category can be found nowhere in the literature.

Proposed Course: The contract is currently beginning the first year of three years of support. The project will be incrementally funded in FY 83 at \$131,637 and in FY 84 at \$148,656.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Section on Nutrition and Endocrinology
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Name of Contractor: UNIVERSITY OF GEORGIA, RESEARCH FOUNDATION, INC.
Athens, Georgia
Ronald R. Eitenmiller, Ph.D. - Principal Investigator
Contract No.: N01-HD-2-2803
Contract Title: Optimization of Human Milk Heat Treatment
Contract Initiation Date: February 1, 1982
Current Annual Level: FY 82; \$45,809

Project Aims: The major objective of this study is to develop optimal conditions for the pasteurization of pooled, mature human milk. The project will first examine the thermoinactivation rate of Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus and Clostridium perfringens in human milk. Simultaneously, it will examine the thermal destruction rate of lactoferrin, vitamin B₁₂ and IgA. Conditions of pasteurization will be based on high temperature short term (ht/st) pasteurization and a batch type pasteurization process. The ht/st procedure is chosen because it is generally less likely to be deleterious to the biologically active factors in milk. One reason ht/st heat treatment has not been extensively investigated in human milk pasteurization is the lack of an appropriate apparatus. This project is designed to solve this urgent need. Optimum temperatures for pasteurization will be derived based on a balance between efficacy in reducing bacterial counts under conditions that have minimal effect on biological properties. Once these conditions are established they will then be examined in terms of efficacy against cytomegalovirus, herpes simplex virus, and rubella virus.

Significance to Biomedical Research and the Program of the Institute: This project represents the first time ever that modern methodologies of high temperature/short term pasteurization have been applied to the study of human milk with the emphasis on retaining as much biological activity as possible while at the same time rendering the milk safe for feeding to infants.

Proposed Course: This contract is early in its first year of support. It will be incrementally funded as follows: FY 83; \$56,270 and FY 84; \$21,928.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Section on Nutrition and Endocrinology
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Name of Contractor: BAYLOR COLLEGE OF MEDICINE
Houston, Texas
Buford M. Nichols, M.D. - Principal Investigator
Contract No.: N01-HD-2-2814
Date Contract Initiated: June 1, 1982
Contract Title: Clinical Studies on Human Milk
Current Annual Level: FY 82; \$289,540

Project Aims: The objective of this project is to assess specific functional consequences of four nutrient sources in the nutritional management of appropriate for gestational age (AGA) premature infants. This clinical study calls for four groups of infants to be compared for differences in outcome as a result of four different courses of nutritional management. The feeding regimens are as follows:

- Group A - Fresh human milk fortified with human milk components
- Group B - Synthetic formula
- Group C - Fresh human milk fortified with non-human milk components
- Group D - Fresh human milk

The infants will be entered into the study at birth and studied intensively for seven weeks with follow-up studies projected over seven months. The fresh human milk fed to all infants will be from their biological mother. The infants in Group A will have their mother's milk fortified with freeze dried human milk cream and dialyzed human skim milk that is low in lactose and adjusted in mineral content to physiological levels. Thus, Groups A, B, and C are comparable with respect to protein in caloric density as well as mineral and electrolyte concentration.

The specific aims of the project are: 1) To assess changes in body composition and rate of growth and development; 2) To assess the maturation of gastrointestinal function by measuring the ability to digest and absorb fat; 3) To assess the bioavailability of nitrogen, sodium, calcium, potassium, manganese and fat in the four nutrient groups; 4) To assess the metabolic responses in terms of clinical tolerance and biochemical indices; 5) To assess bioavailability of immunological factors in banked human milk; 6) To assess maturation and function of the immunologic system; and 7) To assess the influence of milk feeding upon macromolecular absorption.

Significance to Biomedical Research and the Program of the Institute: This project represents the first comprehensive attempt to compare the growth of premature infants fed synthetic formula to a similar group of premature infants fed human milk that is fortified to be comparable with respect to nutrient density and caloric density to that of formula.

Proposed Course: This new project is in the beginning of its first year of three years of support. It will be incrementally funded as follows: FY 83, \$319,211; FY 84, \$297,330.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Section on Nutrition and Endocrinology
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Name of Contractor: HARBOR-UCLA MEDICAL CENTER
Research and Education Institute, Inc.
Torrance, California
Margaret A. Keller, M.D. - Principal Investigator

Contract No.: N01-HD-2-2815

Contract Title: Fractionation, Identification and Characterization of
Components of Colostrum in Human Milk

Date Contract Initiated: June 30, 1982

Current Annual Level: FY 82; \$71,021

Project Aims: The three main objectives of this contract are:

- 1) To determine the functional capability of human milk cells compared to peripheral blood mononuclear cells to produce immunologic mediators as evidenced by lymphokine production when stimulated with the antigen PPD. Lymphocyte derived chemotactic factor (LDCF) will be the lymphokine examined.
- 2) To examine lymphocytes from breast-milk-fed and bottle-fed infants of PPD positive mothers in order to evaluate if data suggest a transfer of cellular immunities via breast milk. Transfer of cellular immunity will be assessed by measuring the ability of the neonatal lymphocyte to produce a lymphokine and to undergo blastogenesis.
- 3) To determine the origin (maternal versus neonatal) of lymphocytes in neonatal circulation that respond to PPD antigen. To do this the chromosomes and the cells of male offspring will be examined by a quinacrine mustard fluorescence method. The working hypothesis is that cellular immunity may be transferred by soluble lymphokines in human milk. The experiments proposed to be carried out are designed to either establish or refute this possibility.

Significance to Biomedical Research and the Program of the Institute: This project is designed to characterize the immunologic properties of human milk with respect to the ability to transfer immunologic factors from the mother to the infant via breast milk.

Proposed Course: The contract is in the beginning stage of the first year of three years of support. It is anticipated that it will be incrementally funded for two additional years as follows: FY 83, \$83,990 and FY 84, \$92,805.

NICHD Annual Report
October 1, 1982 through September 30, 1982
Section on Nutrition and Endocrinology
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Name of Contractor: GEORGETOWN UNIVERSITY
Washington, D.C.
Margit Hamosh, M.Sc., Ph.D. - Principal Investigator
Contract No.: N01-HD-2-2816
Contract Title: Fractionation, Identification and Characterization of
Components of Colostrum in Human Milk
Date Contract Initiated: June 30, 1982
Current Annual Level: FY 82; \$64,739

Project Aims: This project is designed to investigate the lipoprotein lipase and bile salt stimulated lipase activities of mature and pre-term breast milk from the time of birth up to 12 weeks post-partum. In addition, useful information on the effect of lingual lipase on the digestibility of milk lipids in the premature infant will be obtained. Studies will also be carried out to establish optimum storage conditions, i.e., that preserve maximum enzyme activity without changes in enzyme characteristics, the effect of method of milk collection on the level of lipase and fat content in milk and the diurnal variations of lipase levels in pre-term and term milk.

Significance to Biomedical Research and the Program of the Institute: This contract is one of a series of projects designed to establish an expanded the base of knowledge on the composition and characteristics of human milk. This information is essential to future studies on infant nutrition.

Proposed Course: It is projected that this project will be supported for three years. Funding anticipated in future years is as follows: FY 83, \$67,575; FY 84, \$35,360.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Section on Nutrition and Endocrinology
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Name of Contractor: UNIVERSITY OF CONNECTICUT
Storrs, Connecticut
Robert G. Jensen, Ph.D. - Principal Investigator
Contract No.: N01-HD-2-2817
Contract Title: Fractionation, Identification and Characterization of
Components of Colostrum in Human Milk
Date Contract Initiated: June 30, 1982
Current Annual Level: FY 82; \$145,119

Project Aims: This project is designed to collect detailed analytical information on the lipid composition of human milk. The data to be collected include the amount of total solids, nitrogen, non-protein nitrogen, total lipids, triglycerides, cholesterol, cholesterol esters, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine and sphingomyelin. Fatty acids composition of total lipid and of individual lipid classes will also be determined. On selected samples, additional information will be obtained regarding the amount and type of phytosterols and other sterols. Analysis will also be carried out on the molecular species of triglyceride and efforts will be made to identify other polar lipids. These data will be analyzed and compared to dietary information to be gathered on the donors.

Significance to Biomedical Research and the Program of the Institute: This project represents the first time that an in-depth analysis will be carried out on the lipid fraction of human milk. In addition, it will provide the first opportunity to correlate the amount and type of various lipids and free fatty acids with maternal diet.

Proposed Course: This project is beginning its first year of a three year project period. It will be incrementally funded as follows: FY 83, \$161,293; FY 84, \$165,549.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Section on Nutrition and Endocrinology
Clinical Nutrition and Early Development Branch
Contract and Collaborative Research

Name of Contractor: VANDERBILT UNIVERSITY SCHOOL OF MEDICINE
Nashville, Tennessee
Peggy R. Borum, Ph.D. - Principal Investigator
Contract No.: N01-HD-2-2818
Contract Title: Concentration of Taurine, Carnitine and Amino Acids
in Pre-Term and Full-Term Human Milk
Date Contract Initiated: June 30, 1982
Current Annual Level: FY 82; \$113,592

Project Aims: This contract will measure the content of taurine, carnitine and amino acids in milk from mothers delivering pre-term infants and full-term infants. In addition, it will examine the effect of mothers' nutritional status on these parameters as well as the effect of storage of the milk in three different types of plastic containers.

Significance to Biomedical Research and the Program of the Institute: This project is one of a series of projects designed to expand the base of knowledge on human milk. This information is fundamental to ongoing and future projects in the area of infant nutrition.

Proposed Course: This contract is presently starting its first year of three years of support. Funding on an incremental basis is planned as follows: FY 83, \$117,978 and FY 84, \$120,729.

(A) SPECIES-SPECIFIC BEHAVIOR AND BRAIN ORGANIZATION

One investigator is studying how gonadal steroids in gerbils organize brain regions which are essential for a species-specific behavior (territorial marking). The research is also characterizing the critical period for onset of the behavior.

(B) INFLUENCES OF HORMONES ON SOCIAL DEVELOPMENT

Four Institute-sponsored researchers are investigating the involvement of hormones on the development of social behaviors. One scientist is studying the role of aromatized androgens, and a combination of estradiol and DHT on sexual behavior and male aggression in birds. Another is examining how androgens and estrogens affect the development and display of aggression in mice. Two studies on the role of testosterone in the organization of social behavior are underway. The first of these is measuring sexually dimorphic behavior in young rats to determine whether critical periods exist for the role of testosterone in modulating social play. The other study, employing Rhesus monkeys as subjects, is focused upon the relationship of acute endocrine secretion for the social behavior of these primates.

(C) HORMONAL IMBALANCE AND HUMAN BEHAVIORAL DEVELOPMENT

This category of research concerns descriptive analyses of somatic pathology and impaired behavioral development associated with hormonal imbalance. One recently funded study is investigating a cohort of Danish people, now in their early twenties, whose mothers were prescribed progesterone, noresthisterone, or prednisone during pregnancy. The subjects are part of a group of people followed, from birth, in a medical register. The people exposed to these hormones prenatally are being compared to a control group on a variety of behavioral, cognitive, and growth measures. Results of this study will add substantial new knowledge to our understanding of how hormones affect behavioral development and health status.

DEVELOPMENTAL BEHAVIORAL NEUROBIOLOGY

The Institute continues its support of research on brain/behavior relationships. Investigators are using neurobiological approaches, combined with behavioral analysis, to study both animal models and human subjects. Examples of work underway include: neurophysiological and neuroanatomical correlates of learning and behavioral development; electrophysiological correlates of cognitive and behavioral development; brain laterality and cerebral dominance studies; and studies of developing reflexes.

One investigator is employing an invertebrate model to investigate associative learning development at the cellular level. The work demonstrates how conditioning trials can alter the firing pattern of brain cells responsible for locomotion. Two other scientists are studying the effects of rearing conditions on anatomical development of the brain. In one of these projects, a comparison is being made between brain development in rats raised in enriched and impoverished environments.

SENSORY AND PSYCHOMOTOR DEVELOPMENT

Three Institute-supported researchers are investigating the development of the startle reflex. In one study, maturation of the reflex is being measured by recording evoked potentials to loud clicks from scalp electrodes in subjects ranging from 3 to 8 years of age, and in a group of adults. A second investigator, using animal subjects, is experimentally analyzing the eyeblink response to startle stimuli in human adults.

The third series of experiments is analyzing how the nervous system processes such reflex information by studying the unconditional eyeblink in 6- and 8-week-old infants, the startle response in the same subjects, and the elicitation of orienting to startle stimuli.

COMPARATIVE ANIMAL MODELS OF BEHAVIORAL DEVELOPMENT

One area of research, which has received considerable attention, is development of mother-child interaction. Work is focused upon the stress induced by infant-mother separation. Biobehavioral measurements have been used to study the short- and long-term consequences of early separation on emotional development of primates. Other studies have focused upon coping strategies of non-human primates in response to stress. Two possible behavioral mechanisms seem to be employed: (a) flight-fight; or (b) conservation-withdrawal.

COGNITION, PERCEPTION, AND MEMORY

A large portion of the Human Learning and Behavior Branch program in cognitive development is concerned with the abilities and the early development of newborns and infants under a year old. This work encompasses the condition and growth of infants' perceptual abilities, ability to process information, to learn, and to develop concepts. In its totality, this research represents an area of major concentration for the Branch, both in terms of the number of active projects and the funding level. The Branch is equally interested in how perception, attention, information processing, learning, and memory processes develop and change as the child matures, gains experience, and is aided by input from language. Research is, therefore, supported on the development of all of these processes throughout the pre-school years, middle childhood, and adolescence, and into maturity.

INFANCY AND CHILDHOOD

Research on cognition, perception, and memory continues to concentrate on the development of these processes in early infancy. Visual perception has received the greatest attention. Several NICHD-supported researchers are studying the development of visual acuity, and discrimination of intensity or hue. One project involves a study of visual contrast sensitivity function (CSF), the minimal amount of contrast needed to detect a pattern in the spatial frequency of a repeating stimulus. The results indicate that infant's pattern sensitivity, which develops significantly over the first three months of life, is quite different from adult sensitivity. Other work, now ongoing, is investigating how sensorimotor mechanisms develop, and their relationships to perception. For example, research has shown that the accuracy of visual accommodation improves greatly during early development and reaches near-adult levels by 3 to 4 months. Several researchers are also examining the acquisition of coordinated eye and head movements toward visual targets.

Research is also being conducted to discover how the senses of vision and hearing become coordinated. For example, one study is examining the neonate's preference for visual objects which are correlated with temporally synchronized sounds. Institute-supported research has also demonstrated that 3- to 6-month-old babies discriminate figure from ground, only if there is a spatial separation between the two. Such research is crucial for understanding how infants develop the concept of objects.

Perception of spatial orientation of two and three dimensional forms is the subject of research by several investigators. One has found that orientation perception

proceeds through three levels of development. Children first distinguish between upright and non-upright shapes; then discriminate non-upright shapes as upside down or sideways. At a third level, sideways shapes are identified as right- or left-turned. Another study involves perception of large-scale space as it develops during childhood, the child's use of landmarks and cues, and an estimation of distance.

The Institute is also supporting several studies on the development of memory. Infant's preference for novel objects is used by investigators to test memory span. For example, results of experiments using preferential looking demonstrate that 7- and 8-month-olds remember stimuli presented 24 hours before. Researchers are also studying how children develop encoding skills and retrieval strategies (mnemonics) to improve the amount remembered. In addition, work is underway to examine how a child's knowledge about memory processes (metamemory) affects the ability and capacity to remember.

ADOLESCENCE

Research on cognition has focused increasingly on developmental topics which span childhood, adolescence, and adulthood. For example, one study of cognitive development, from early childhood through adolescence, examined the effects of an early-enrichment program (Head Start) on later cognitive and social development in adolescence. Results demonstrate that black boys who participated in a non-didactic (Montessori) preschool program had significantly higher IQ scores in the 6th, 7th, and 8th grades than did a similar cohort of boys who were enrolled in a didactic program when they were preschoolers. Specific characteristics of the programs, which are most beneficial to boys have yet to be determined, although the Montessori program is noted for emphasizing individualization, work habits, and initiative.

The Branch also supports studies on the development of scientific thinking in children. For example, information processing experiments and tests of Piagetian theory have been designed to gain an understanding of number concepts, biological concepts, and time and proportionality concepts. By assessing the kinds of implicit rules children use, investigators can compare across dimensions and age groupings. Results suggest that problem-solving ability depends on how children structure their existing knowledge, and what type of strategy they use to solve the problem.

SOCIAL AND AFFECTIVE DEVELOPMENT

The program of the Branch in social and affective development covers a broad range of important research issues. It is concerned with the process of socialization of the child, both within and without the family, from infancy to adolescence and early adulthood. Also included within the program are studies on the relation of affect, temperament, and personality to social and biological factors during development.

INFANCY AND CHILDHOOD

Personality and temperament are two variables which are known to affect problem-solving ability in social situations. For example, one Institute-sponsored researcher has studied the role of self regulation in the development of delay of gratification. Individual differences observed from birth are also deemed important, since they appear to significantly influence the quality of mother-child interaction. Along these same lines, other researchers are studying how the personality characteristics of the parent can affect the development of infant temperament qualities such

as responsivity and ability to be soothed.

Another area of interest continues to be the development of gender identity. One investigator is studying sex differences in a cohort of children from birth through the first grade. Results indicate that there are significant differences between boys and girls on measures of muscle strength, sleep patterns, and timidity. However, these differences cannot predict behavioral development. The research also demonstrated that early differences in play behavior between boy and girl babies depends upon situational factors, such as the amount of space available and the gender of a child's playmate.

A number of studies are supported by the Institute on development of peer interactions. One researcher, for example, has extensively studied toddlers' spontaneous acts of helping and sharing, and has developed a scale of normal social development in the first three years of life. He has also detailed effects of adults' instruction, rewards, prompts, and modeling on such prosocial behavior. Another group of investigators is studying those behaviors and skills which enter into the development of successful peer interactions at different ages. Results, to date, indicate that friendships, while marked by mutuality and reciprocity, also seem to promote competition. Age differences are, of course, important in determining children's peer interactions. For example, results from one study indicate that the presence of an unfamiliar peer inhibits exploration in 18-month-olds, but promotes it in 30-month-olds. Based upon the findings of another NICHD researcher, the generalization emerges that dominance in children's interactions is determined mainly by social competence rather than aggressiveness. Children's beliefs and expectancies are also under study in relation to helpful and altruistic behaviors. Two researchers are examining the dynamics of interactive groups by varying their composition to increase interactive behavior. Results from one of these projects reveal that pairing a shy, "isolate" child with slightly younger children increases his approaches to age-mates.

ADOLESCENCE

Adolescence, the period of development between the ages of 10-20 years, has been singled out for special consideration by the Institute. Research currently supported includes studies on development of aggression, gender-identity, psychological development at puberty, and transition to adulthood.

Work on the development of aggression is being carried out in the context of a study on children in grades 1-10. Observations are being made of strategies, used by them, at different ages to control potentially aggressive behavior in both naturalistic and laboratory settings. Results, to date, indicate that, among males, aggressive behavior is the most typical pattern observed. Gender identity and changes in self-concept are being studied in 6th-9th grade girls who are approaching and experiencing the onset of menarche. The research is focusing upon developmental changes in body-image, self-concept, and psychological well-being in connection with this physiological milestone.

Developmental issues, related to late adolescence and the transition to adulthood, are the subject of research by Institute-sponsored investigators. One new study, for example, is examining the social network supports and coping behavior of young adults (college graduates) in their transition to job entry, marriage, and parenthood. Network cohesiveness, individual adjustment and well-being, and spacing between transitions are hypothesized as important determinants of successful coping

During the transition to adulthood. Another recent study is following-up individuals, 15 years after high school, to determine what factors contribute to their development of social and psychological well-being. Measures include scales of satisfaction with job, marriage and parenthood, and a global measure of life satisfaction.

THE FAMILY

Despite continuing changes in its structure and function, the family remains a predominant socializing force. Family influences, either explicitly or indirectly, effect the child's development in cognition, language, and social behavior. The specific dynamics of family functioning, that is, the relationship of family members to one another, and the relationship of the family to the outside community, are also research topics of great interest to the Institute.

Currently the Branch funds a modest number of projects which focus upon the development of sibling relationships, and the coping mechanisms employed by families to deal with stress. One newly funded study is examining interaction patterns of siblings within the family unit in relation to their gender, ordinal position, and age. The investigator is employing cohorts at three developmental periods (elementary, intermediate, and high schools). Another project involves a cross-national study of families' use of informal social networks to deal with stress. A preliminary analysis of U.S. data, based on two pilot neighborhoods, indicates that shifts, during the past three years, in marital status, residential mobility, and employment changes are associated with changes in the network membership of mothers. Separation and divorce trends, for both mothers and fathers, have resulted in a shift from kin to non-kin centered networks. Moreover, when mothers work outside the home, membership non-kin networks increased significantly. The data indicate that such new affiliations provide the parent with additional emotional support.

COMMUNICATION ABILITIES

The scientific study of speech and language calls for a multifaceted, multidisciplinary approach, within the context of a systems analysis. Such a model identifies three categories of variables: (a) input, (b) processing, and (c) output. Input consists of physical stimuli (sights and sounds) and sensory modalities (vision and hearing) involved in the reception of the necessary and sufficient information for communication to occur. Processing consists of the storage, retrieval, and interpretation of the information received, and output involves the use of the processed information by the receiver to guide behavior.

NICHHD supports research covering each of these aspects. For example, the input stage of speech and language is within the domain of electrical engineers and psychoacousticians who study the physical characteristics of speech sounds. Working along with such researchers on the input side of communication are an array of scientists who study the receptor channels through which information passes prior to processing. Sensory physiologists and neuroscientists are conducting research, using animal models, to elucidate the anatomy and physiology of the visual and auditory systems. Psychophysicists are exploring the dynamics of these sensory modalities to characterize what the neonate is capable of hearing and seeing. Investigators involved in studying processing employ methods from the cognitive science tradition. Experiments are designed to discover and analyze the behavioral mechanisms which support short- and long-term memory and access to such stored information. Neuroscientists are also keenly interested in this stage of the communica-

tion process. Using modern electrophysiological recording techniques, in conjunction with computer analysis, they assess the dynamics of processing of input by analyzing the frequency and amplitude of brain electrical activity. Much progress has been achieved during the past decade identifying, with these methods, loci within the brain where processing occurs, and mechanisms involved in encoding and retrieval. Work is also underway to characterize the development of brain lateralization for language processing.

Research on the output side of the model centers upon articulation, pattern and rhythm of speech, and a formal analysis of the rules of language. Along with such analysis, linguists apply scientific methods and mathematical models to elucidate the syntax and grammar of language to determine the guidelines employed by "language communities" to enhance precision and predictability in and of speech and language.

The program includes research on the development of speech and language and reading ability. For example, studies focusing upon precursors of language in normal children are underway. Investigators have described temporal patterning of crying and other types of produced sounds early in life. Such information can clarify whether early vocalizations are necessary experiential components for later acquisition of speech and language. In the area of psycholinguistics, NICHD-sponsored scientists are making excellent progress in understanding the infant's production and perception of speech. Using linguistic analysis techniques, along with modern acoustical methods, such research is providing detailed descriptions of how infants encode parameters of parts of speech, such as vowels.

A substantial investment in research on reading continues to be a hallmark of the Institute program on communications abilities. Several Institute-supported scientists are studying how children learn to read. Such work involves research on the role played by eye movements, fixation, and visual processing of written text.

A special emphasis area of the communications abilities program is dyslexia, an acknowledged learning disability of public health relevance. This puzzling disorder affects children's ability to acquire the skills of reading and writing, and can markedly influence the potential for learning and effective school performance. The Institute, therefore, supports a wide array of research projects to develop basic knowledge on this topic. For example, work is underway to determine the genetic and sexually dimorphic factors associated with dyslexia (most dyslexics are males). Other investigators have begun to describe subtypes of the disorder. Such findings reinforce the view that multiple mechanisms are involved in its etiology. Neuroscientists have described electrophysiological correlates of processing written material on dyslexics.

BEHAVIORAL PEDIATRICS

The growing recognition that behavioral factors play a significant role in the etiology and treatment of illness, as well as in the maintenance of good health, has given rise to a new field of scientific endeavor, behavioral medicine. Under this broad rubric, the research efforts of the Institute are best subsumed by the name, Behavioral Pediatrics. Within this program area, NICHD-supported scientists are studying issues which are broadly grouped under the headings of: health behavior, illness behavior, and risk-taking behavior.

HEALTH BEHAVIOR

Included in this category is research on individual and socio-environmental factors

which contribute to the acquisition and maintenance of behaviors which optimize healthy development. Currently supported work is focused upon mothers' pattern of medication use for their children's illness and health promotion in young children. Preliminary results from the study on use of medications indicate that middle-class mothers purchase nearly twice as much over-the-counter drugs as do lower-class mothers. An innovative health education program on nutrition, safety, and smoking is being developed, in a predominantly black and hispanic community, for preschool children and their families. The goal of the project is to measure the acquisition and maintenance of health-related behaviors in these children during the course of their development, and to assess their health status through elementary school.

ILLNESS BEHAVIOR

Included in this category are studies of factors which influence the psychosocial and bio-behavioral adaptation of the child and its family to illness, hospitalization, pain, and stress. Examples of supported research include an investigation of the psychosocial adjustments of families with children who have diabetes mellitus, and an analysis of parents' response to Cesarean section delivery. Results from this latter study indicate that, compared to other SES categories, lower-class men, whose wives had undergone Cesarean section, were more involved in child care. This trend was observed even one year after the birth of the child.

RISK-TAKING BEHAVIOR

This category includes studies designed to further an understanding of behaviors which are harmful to health, such as the use of cigarettes, eating disorders, and accident-proneness. Research related to risk-taking behavior continues to be the largest component in Behavioral Pediatrics due primarily to a Department of Health and Human Services initiative three years ago on prevention research which emphasized deterring cigarette smoking in children. Currently, the Institute supports 11 studies on children's smoking behavior.

A significant outcome of this program is the agreement, among investigators, to use biochemical markers, such as saliva thiocyanate and plasma cotinine to provide objective measures of smoking activity. Results from one investigator, who is using saliva thiocyanate to validate self reports of smoking among 7-12th graders, indicate that the incidence of cigarette smoking among this group may not be declining, as reported by previous surveys based solely on self reports. The role of social influences, in the onset of smoking, is another important issue being studied.

Findings demonstrate that adolescents generally smoke their first cigarette in the presence of other people (family, peers). Among regular adolescent smokers, girls tend to smoke more often than boys in social situations, especially when they are with girls of the same age. Other researchers have found that adolescents who strongly value independence believe that smoking will make them more socially dominant. Knowledge of these factors can provide important insights on how to best design smoking cessation intervention programs for youngsters.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Human Learning and Behavior Branch
Contract and Collaborative Research

Contract Number: N01 HD-1-2420

Contract Title: Research Materials and Assistance for Studies of
Language Development in Children

Contractor: Haskins Laboratories, New Haven, Connecticut
Alvin M. Liberman, Ph.D.

Money Allocated: \$108,690.00

The purpose of this contract is to continue to provide expert assistance and specialized facilities to research scientists at other institutions who are engaged in studies relevant to an understanding of the development of spoken language and reading in children.

In general, three kinds of assistance have been provided to researchers working on problems related to the acquisition of speech and reading.

1. Research Materials. Stimulus tapes for a wide variety of experiments continue to be the primary assistance that the Laboratories have provided. Several methods of generating recordings suitable for research on speech are available. The techniques can be grouped either by type of stimulus (natural speech, synthetic speech, or nonspeech tones and noises) or by type of recording (single track or dual track). All combinations of these tapes have been used for one research project or another.

2. Specialized Assistance. The professional and technical staff of Haskins Laboratories makes its knowledge and skill available to the user groups. At the very least this involves having someone from the technical staff teach the user group how to operate the computer. But it often involves, beyond that, getting various kinds of help and advice about the more scientific aspects of the research from members of the Laboratories' professional staff. In the end, the user group generates its own tape recordings.

3. Education about Speech Research. A rather high percentage of the user groups are fairly new to the field of speech. Consequently, as a by-product of their visits to the Laboratories, they have an opportunity to become better acquainted with the entire program of research underway there. Many have taken advantage of that opportunity.

With a team of senior scientists the Institute visited the Haskins Laboratories in September of 1979 to examine the activities supported by this contract. Without exception these reviewers recommended approval of the request for three years of additional support. There was general agreement that the service and assistance provided by the contract had been helpful to many investigators, most of whom would not have been able to otherwise conduct their proposed research.

NICHD Annual Report

October 1, 1981 through September 30, 1982

Office of the Director
Epidemiology and Biometry Research Program

The Epidemiology and Biometry Research Program conducts investigations of disorders of mothers and children, of perinatal mortality and morbidity, of low birth weight, infant feeding and abnormalities of human growth and development. The Program also provides statistical and epidemiological consultation to intramural scientists and to the staff of the extramural programs of the Institute as well as to other government agencies and representatives from universities and private institutions.

In January 1982 the Computer Sciences Unit was formally established as the Section on Computer Sciences which serves as the focal point for expertise in the computer sciences in the Institute in addition to continuing its support to the research program of the EBRP. Several staff members of the Office of Program Planning who are providing support for data systems to the extramural programs were transferred to the new section.

Dr. George Rhoads has accepted the position as Chief of the Epidemiology Branch and will join the program on September 7, 1982. Dr. Rhoads comes from the University of Hawaii where he was Professor of Epidemiology. In addition Dr. Samuel Kessel joined the program in October 1981. Dr. Kessel is a pediatrician, formerly with the Office of the Assistant Secretary for Health, who is currently enrolled at the School of Public Health at Johns Hopkins where he is expected to obtain his master's in epidemiology in January 1983. Also Dr. Mark Klebanoff joined the Program July 1, 1982, as an epidemiological training officer. Dr. Klebanoff is also at the School of Public Health at Johns Hopkins in the Master's of Public Health program.

The pilot study of a case control study of factors associated with low birth weight children at Howard University has been completed, and the protocol revised. EBRP has requested a support contract to obtain the services of interviewers and abstractors for the full implementation of this study in six major hospitals in the District of Columbia.

The Diabetes in Early Pregnancy study is continuing and recruitment of both diabetic and non-diabetic women has been successful. The study is progressing well.

To evaluate long term effects of a chloride deficient formula marketed as Neo-Mull-Soy in 1980 the program has issued an RFP in pursuit of this objective.

EBRP staff has participated in discussions with the Centers for Disease Control regarding a clinical trial of multi-vitamins and/or folate and its

role in the prevention of neural tube defects. EBRP staff also has discussed with staff of the Center for Research in Mothers and Children participation in a study to address comprehensively the question of infection during pregnancy and the risk of low birth weight as well as preterm delivery.

EBRP staff is exploring the feasibility of studying the outcomes of human in vitro fertilization. Such a study would include success rates, fetal loss rates after successful implantation, congenital malformations and the physical growth and development of live born children.

The NICHD has been involved in the treatment of precocious puberty with analogues of luteinizing hormone releasing hormone (LHRH). Drs. Mills and Berendes will discuss plans for monitoring long term effects of these compounds with Drs. Loriaux and Cutler from the intramural program.

Dr. Mills is currently involved in defining normal levels in early pregnancy for prolactin, testosterone and human chorionic gonadotropin. These values will be compared with values seen in diabetic women over the same period of gestation. Dr. Mills will collaborate in the study examining factors which influence the development of anti-insulin antibodies in diabetes. He will also address the problem of identifying oral contraceptive workers who have been contaminated by hormones. Finally he will examine possible teratogenic effects of acetaminophen used during pregnancy.

Dr. Berendes has forwarded an outline of a study of pregnancy outcome including low birth weight, neonatal mortality and congenital malformations in Shanghai County, China. This proposal has been sent through official channels and when implemented would provide detailed information on the characteristics of pregnancy and pregnancy outcome of approximately 10,000 pregnancies occurring in Shanghai county per year. This study is of considerable interest because of the reported low rate of low birth weight in certain areas of China including Shanghai county.

Dr. Mills presented a paper at the Plenary Session of the Society for Epidemiological Research, Cincinnati, Ohio, in June 1982, entitled "Are Spermicide Teratogenic." He lectured at Johns Hopkins University on Diabetes in Early Pregnancy and participated as a workshop leader in discussions on malformations in infants of diabetic mothers at the American Diabetes Association in Chicago, 1981. Dr. Berendes participated in a symposium at Johns Hopkins in November 1981 entitled "Changing Health Problems in Women" where he presented a paper on the health effects of oral contraceptives which is to be published as part of the proceedings. He completed with collaborators from Johns Hopkins University, University of Southern California and University of California in San Francisco the analysis of data on the relative risk of pituitary adenoma associated with oral contraceptives. The paper has been completed and submitted for publication. He is further involved in the development of a monograph to be completed during the fall of 1982 which will present data from a large cohort study addressing possible health effects of vasectomy.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00323-2 EBRP																												
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SUMMARY OF WORK (200 words or less - underline keywords) <p style="text-align: justify;"> This is a case control study of factors associated with the birth of low birth weight and preterm children delivered in the Washington, D.C., area. The study is proposed to include eventually all live birth low birth weight and preterm deliveries at the six major obstetrical services in the District of Columbia and of controls which will provide approximately 90% of all births in the District of Columbia. The pilot study has been completed at Howard University. Problems which have been identified during the pilot have to do with difficulties in obtaining hospital records and prenatal clinic records on some women, identifying questions in the interview which most women cannot answer, evaluating the appropriateness of responses and other similar issues. As a result of the findings from the pilot revision of the questionnaire and protocol has taken place. It is proposed to implement the study in all hospitals in the near future pending approval of a request for a support contract which would provide for interviewers and abstractors to obtain the information on cases and controls. </p>																														

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SECTION																		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD.																		
TOTAL MANYEARS: .5	PROFESSIONAL: .5	OTHER: 0																
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																		
SUMMARY OF WORK (200 words or less - underline keywords) <p>Diabetes Mellitus is known to be associated with certain HLA types. It is also known to cause <u>malformations</u> in infants of diabetic mothers. This study will examine the relationship between HLA "markers" for diabetes and malformations.</p> <p>The retrospectively ascertained study groups have been HLA typed. There is evidence of a "protective" effect in the DR locus. Although this finding is significant, a prospectively ascertained population is being enrolled to confirm this finding.</p>																		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00319-02 EBRP
PERIOD COVERED October 1, 1981 through September 30, 1982		
TITLE OF PROJECT (80 characters or less) Umbilical Cord Growth		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
James L. Mills	Medical Staff Fellow	EBRP NICHD
Heinz W. Berendes	Director	EBRP NICHD
Ernest E. Harley	Supervisory Computer Specialist	EBRP NICHD
Adrian Moessinger	Asst. Prof. of Pathology	College of Physicians and Surgeons
William Blanc	Professor of Pathology	College of Physicians and Surgeons
COOPERATING UNITS (if any) College of Physicians and Surgeons, Columbia University		
LAB/BRANCH EBRP		
SECTION		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD		
TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) <p style="margin-left: 40px;"> <u>Prenatal growth</u> of the human umbilical cord is being assessed using data from the Collaborative Perinatal Project. Standards for normal growth have been derived from these data. </p>		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00321-02 EBRP
PERIOD COVERED October 1, 1981 through September 30, 1982		
TITLE OF PROJECT (80 characters or less) Teratogenic Effect of Spermicides		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
James L. Mills	Medical Staff Fellow	EBRP NICHD
Heinz W. Berendes	Director	EBRP NICHD
Ernest E. Harley	Supervisory Computer Specialist	EBRP NICHD
COOPERATING UNITS (if any)		
LAB/BRANCH EBRP		
SECTION		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD		
TOTAL MANYEARS: .6	PROFESSIONAL: .6	OTHER: 0
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords)		
<p>Data from the Walnut Creek Contraceptive Study is being examined to determine whether or not <u>spermicide</u> use is associated with <u>congenital malformations</u>. Malformation rates in women exposed to spermicides either before or after conception are being compared with rates in users of other (or no) contraceptives.</p>		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00325-01																
PERIOD COVERED October 1, 1981 through September 30, 1982																		
TITLE OF PROJECT (80 characters or less) Neural Tube Defects and Folate																		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0" style="width: 100%;"> <tr> <td style="width: 33%;">James L. Mills</td> <td style="width: 33%;">Medical Staff Fellow</td> <td style="width: 10%;">EBRP</td> <td style="width: 24%;">NICHD</td> </tr> <tr> <td>Heinz W. Berendes</td> <td>Director</td> <td>EBRP</td> <td>NICHD</td> </tr> <tr> <td>Samuel S. Kessel</td> <td>Medical Officer</td> <td>EBRP</td> <td>NICHD</td> </tr> <tr> <td>Godfrey Oakley</td> <td>Chief, Birth Defects Branch</td> <td>CDC</td> <td>Atlanta</td> </tr> </table>			James L. Mills	Medical Staff Fellow	EBRP	NICHD	Heinz W. Berendes	Director	EBRP	NICHD	Samuel S. Kessel	Medical Officer	EBRP	NICHD	Godfrey Oakley	Chief, Birth Defects Branch	CDC	Atlanta
James L. Mills	Medical Staff Fellow	EBRP	NICHD															
Heinz W. Berendes	Director	EBRP	NICHD															
Samuel S. Kessel	Medical Officer	EBRP	NICHD															
Godfrey Oakley	Chief, Birth Defects Branch	CDC	Atlanta															
COOPERATING UNITS (if any) CDC - Atlanta, Georgia																		
LAB/BRANCH EBRP																		
SECTION																		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD																		
TOTAL MANYEARS: 1.0	PROFESSIONAL: .8	OTHER: .2																
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																		
SUMMARY OF WORK (200 words or less - underline keywords) <p>The EBRP and CDC staff are examining the feasibility of a pilot study to investigate the relationship between maternal folate deficiency and neural tube defects. Defining a suitable population, devising a workable study design and determining the cost of performing the study are the current goals.</p>																		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00326-01 EBRP
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PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Premature Thelarche on Puerto Rico

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

James L. Mills	Medical Staff Fellow	EBRP	NICHD
Heinz W. Berendes	Director	EBRP	NICHD
Godefrey Oakley	Chief, Birth Defects Branch	CDC	Atlanta

COOPERATING UNITS (if any)

LAB/BRANCH
EBRP

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, MD

TOTAL MANYEARS: 6	PROFESSIONAL: 6	OTHER: 0
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Data from the Walnut Creek Contraceptive Study is being examined to determine whether or not spermicide use is associated with congenital malformations. Malformation rates in women exposed to spermicides either before or after conception are being compared with rates in users of other (or no) contraceptives.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Office of the Director
Epidemiology and Biometry Research Program

Contract and Collaborative Research

Project Title : Malformations and Fetal Losses in Pregnancy in Women With Juvenile Onset Diabetes Mellitus

Contractors : The Boston Hospital for Women, Cornell University Medical Center, The University of Pittsburgh, Northwestern University Medical Center, and The University of Washington

Money Allocated:	Boston Hospital for Women	\$149,608
	Northwestern University	169,831
	University of Pittsburgh	126,385
	Cornell University	134,717
	University of Washington	217,810

Objectives : Performing a prospective collaborative study

1. To examine the relationship between maternal diabetic control during organogenesis and malformations in the offspring. To identify, if possible, a specific teratogenic factor or factors in the diabetic metabolic state;
2. To compare early fetal loss rates in women with diabetes and control subjects.

Significance to Biomedical Research and the Program of the Institute: The incidence of malformations in offspring of juvenile diabetic women is believed to be at least twice that of normal women. The early fetal loss rate in diabetic women has not been determined. This study will search for a teratogenic mechanism in diabetes and attempt to determine whether good diabetic control during organogenesis can prevent these excess malformations. In addition, it will be determined whether or not diabetic women have increased losses early in pregnancy.

Proposed Course: The study is now in the field. NICHD will continue to direct the conduct of the study. Specific objectives include: stimulating recruiting efforts, maintaining strict quality control and accurate data reporting and preparing the analysis phase of the study. Preliminary analysis is now underway.

Project Officer: James L. Mills, M.D., M.S.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Office of the Director
Epidemiology and Biometry Research Program

Publications

Mills, J. Stolley, P., Davies, J., and Moshang, T.: Premature thelarche: Natural history and etiologic investigation. American Journal of Diseases of Children 135:743-745, 1981

Stanley, C., Mills, J., and Baker, L.: Intra-gastric feeding in type I glycogen storage disease: Factors affecting the control of lactic acidemia. Pediatric Research 15:1504-1508, 1981

Mills, J.: Malformations in infants of diabetic mothers. Teratology 25:385-394, 1982

Mills, J., Harley, E., Reed, G., Berendes, H.: Are spermicides Teratogenic? Journal of American Medical Association - In Press

NICHD Annual Report
October 1, 1981 through September 30, 1982
Office of the Director
Epidemiology and Biometry Research Program

Presentations

Malformations in Infants of Diabetic Mothers:

Can They Be Prevented?

Workshop Leader

American Diabetes Association

Northern Illinois Affiliate

Chicago, Illinois

October, 1981

Diabetes in Early Pregnancy

Johns Hopkins University

School of Public Health

Baltimore, Maryland

April, 1982

Are Spermicides Teratogenic?

Plenary Session

Society for Epidemiologic Research

Cincinnati, Ohio

June, 1982

NICHD Annual Report

October 1, 1981 through September 30, 1982

Biometry Branch

The Biometry Branch continued activities along three lines: (1) provision of statistical analysis and consultation to NICHD Intramural and Extramural investigators; (2) pursuit of individual and collaborative research in biometry and biostatistics; and (3) support of clinical trials initiated by the NICHD. The Branch maintained its traditional strong ties to both the Intramural and Extramural programs of the Institute. Also, the Branch has supported a number of cooperative projects, including projects supported solely by NICHD and those receiving joint funding from other agencies within the Department of Health and Human Services.

This year a major effort has been invested in support of the NICHD Cooperative Epidemiological Study of Sudden Infant Death Syndrome (SIDS) Risk Factors. The first reports of preliminary findings based on this study were presented to the Annual Meeting of the American Pediatric Society - Society for Pediatric Research (APS-SPR) held in Washington, D.C. in May, 1982. The design of this large scale cooperative case-control study was presented by Mr. Howard Hoffman, Chief of the Biometry Branch, and Assistant Project Officer, for the contracts which have supported this study. Dr. Eileen Hasselmeyer, Project officer, and Mr. Jehu Hunter, Study Coordinator, also presented papers at this Symposium. In all, twelve papers were presented covering the initial findings from the first 400 cases and 800 matched living controls. Preliminary results from the interview schedule and medical and pathology records data were discussed. Also, an abstract outlining the prenatal and neonatal medical factors in relation to SIDS was published in the April program issue of the Journal for Pediatric Research.

Prior to the APS-SPR meeting, NICHD program staff for the SIDS Cooperative Study (Dr. Hasselmeyer and Mr. Hoffman) prepared a press release concerning the hypothesized relationship between DPT inoculation and SIDS occurrence. Findings from the NICHD SIDS Cooperative Study were negative in that more controls than cases (2% vs. 1%) had received DPT shots less than 24 hours prior to interview or death. Only 38% of SIDS cases among the first 400 had ever been immunized for DPT, compared with 57% for the age, race, and birth weight matched living control infants. Similar percentages were noted for infants receiving polio vaccine. These data refute the notion that DPT immunization is related to SIDS etiology which was strongly implied by Dr. William Torch's presentation at the American Academy of Neurology Meeting in Washington in April, 1982. Dr. Hasselmeyer released the preliminary findings from the NICHD SIDS Cooperative Study concerning DPT at this meeting in the discussion following Dr. Torch's paper. Several distinguished neurologists also took issue with the design and other methodological aspects of Dr. Torch's study, both in the discussion of his paper and at a subsequent news conference organized by the Academy. Later in May, Mr. Hoffman presented an invited paper on "SIDS and DPT" which reiterated the NICHD SIDS Cooperative study's preliminary negative findings to the 17th Immunization Conference at the Centers for Disease Control in Atlanta, Georgia.

The reporting of preliminary findings from the NICHD Cooperative SIDS Study will continue with an invited symposium for the Epidemiology Section of the American Public Health Association in the fall of 1982. Both Mr. Hoffman and Dr. Berendes are planning to make presentations on the study results at this meeting. In June, 1982, Mr. Hoffman and Dr. George Reed attended the International Research Conference on Sudden Infant Death Syndrome held in Baltimore, Maryland, which was jointly sponsored by the University of Maryland SIDS Institute and the British Association for the Prevention of Crib Death. This meeting provided an opportunity to assess the current state of knowledge regarding SIDS etiology from research studies underway in various countries. Dr. Berendes and Mr. Hoffman also attended a mini-Steering Committee meeting for the NICHD SIDS Cooperative Study which was held in Baltimore, the day after the International Research Conference concluded.

Another cooperative study in which Biometry Branch staff have contributed extensive time and effort to during the past year is the Diabetes in Early Pregnancy Study with Dr. James Mills, Project Officer, EBRP. Mrs. Dolores Bryla serves as Study Coordinator and Dr. George Reed is the Project Statistician. This study is a prospectively-designed clinical investigation to determine the incidence rates of early fetal loss and congenital anomaly in the conceptuses of juvenile-onset diabetic mothers and non-diabetic control mothers. Furthermore, this study will test whether tight diabetic control is a factor in ameliorating the otherwise expected high rates of fetal loss and/or congenital anomaly. Nearly half of the projected women have now been enrolled in the study, although it is too soon to report on the preliminary results.

Another cooperative study which has involved a large amount of Biometry Branch staff time is the Randomized, Controlled Study of Phototherapy for Neonatal Hyperbilirubinemia with Dr. James B. Sidbury, Project Officer and Scientific Director, IRP. Mrs. Dolores Bryla has devoted a significant percentage of her time to the data management and analysis of this on-going project. Ms. Leigh Baker was hired again for the summer to help expedite the data editing and updating of the sixth-year follow-up examination forms. The sixth-year examination is a comprehensive one, including physical, neurological, psychological and audiology data. Originally, 1,339 patients were admitted to the study and randomized to either the phototherapy or non-phototherapy treatment groups. Manuscripts have been prepared for the analysis of the newborn data by the study's principal investigators. Topics included were the efficacy of phototherapy, neonatal and infant death rates, rates of exchange transfusion required, hemolytic disease rates, associations with small-for-gestational age, serum-binding studies, other metabolism studies, photodosimeter badge data, and a survey of phototherapy use. In addition to preparing these papers, analyses have begun on the physical, neurological and mental development testing which was done at one year. The histories and physical examinations performed on these children at 2, 3, 4, and 5 years of age are already coded and on computer tape for future data analysis.

The Biometry Branch also serves as the Data Center for the National Cysteamine Study, a clinical investigation of the efficacy of the drug cysteamine as a therapy for cystinosis. Dr. George F. Reed assumed responsibility of directing the data center this past year. He has been assisted by Mr. Daniel Denman in the generation of updates and interim analysis of accumulating data. Also, a graduate student in Biostatistics, Ms. Olivia Carter, has worked this summer on cleaning and editing of the data. This

study is being done in collaboration with Dr. Joseph D. Schulman, Chief, Human Biochemical and Developmental Genetics Section, NICHD, and with two other principal investigators, Dr. Jerry Schneider, UC-San Diego Medical School and Dr. Jess Thoene, University of Michigan Medical School. Dr. James Schlesselman continues to provide statistical consultation since moving to his new position as Associate Professor, Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences.

In beginning this clinical trial, it was felt that cysteamine would act as an agent for inhibiting or reversing the nephropathy associated with cystinosis. To date, the renal function of nearly 70 treated patients has been followed for an average of 14 months per patient. These data have been compared to historical placebo controls taken from an earlier clinical trial of the efficacy of vitamin C in treating cystinosis. The latter data have recently been characterized using statistical and graphical techniques to provide age-specific baseline information by Drs. George Reed, William Rizzo, and Joseph Schulman. At this point there is no strong positive effect attributable to cysteamine therapy, but a somewhat longer follow-up period will be required to reach any firm conclusions.

Although the preceding four studies represented a major component of Biometry Branch support for the Intramural and Extramural programs of the Institute, a number of other consultations occurred with NIH and other research investigators, a summary of several being as follows.

Mr. Hoffman, Dr. Reed and Ms. Carter were asked by Dr. Donald Mattison, Pregnancy Research Branch, to advise on problems in bio-assay to detect differences with respect to ovarian toxicity between several constituents of cigarette smoke.

Mr. Hoffman, Mr. Graubard and Mr. Sahlroot also have consulted with Drs. Leon Yarrow, David Messer, Robert MacTurk and Mary McCarthy of the Child and Family Research Branch in regard to their longitudinal data file on children aged 6, 12, and 30 months to identify elements in mastery motivation development. A variety of multivariate analysis techniques have been used on these data, including cluster analysis, factor analysis, and regression analysis, to attempt to sort out the complex relationships.

Mr. Graubard and Mr. Hoffman have also consulted with Drs. Elaine Neale and Phyllis Sher, Laboratory of Developmental Neurobiology, with regard to the analysis of their data on the growth of neuronal cells from the cerebral cortex of fetal mice in tissue culture dishes when anti-convulsant drugs are added to the medium. Analysis of covariance has been used as the principal statistical technique for this collaboration.

Mr. Hoffman and Mr. Denman have consulted with Drs. Mary Ann Brock and James Nagle, Clinical Physiology Branch, NIA, on data reflecting seasonal and age-related effects in the immune defense system based on the longitudinal study of human physiological data collected at the Gerontology Research Center in Baltimore. Mr. Hoffman and Mr. Denman have also been involved in a collaboration with Dr. Barry Bercu and co-workers, Neonatal and Pediatric Medicine Branch, on developing statistical time series analysis methods appropriate for studying hormonal series of moderate length. This collaboration resulted in two papers being prepared and two presentations being given to scientific

meetings.

Mrs. Overpeck, Dr. Berendes, Mr. Hoffman, and several other members of the Branch have been involved in consultations with Mrs. Gail Poe, Mrs. Mary Grace Kovar and Mr. Robert Fuchsberg, Division of Health Interview Statistics, NCHS, regarding the data editing and future analysis of the 1981 Child Health Supplement to the Health Interview Survey. Several meetings were held between our combined staffs to discuss priorities for data management as well as research objectives.

Dr. Reed collaborated with Dr. Mills, Dr. Berendes, and Mr. Harley, EBRP, on a project investigating the potential teratogenicity of spermicides. The data analyzed were from the NICHD Kaiser-Permanente Birth Defects Study, and no association was found between spermicides and increased risk of either major or minor birth defects.

Also, Dr. Reed participated with Drs. Bercu, Corden, Rizzo and Schulman, Pediatric and Neonatal Medicine Branch, on a study reporting the observed differences in somatomedin C levels in cystinotics when compared to normal control children.

Dr. Reed was also engaged in a consultation with Dr. Bruce Stadel, Contraceptive Evaluation Branch, on a case-control study of the association between different oral contraceptive formulations and the risk of myocardial infarction. This material is currently being written up for publication.

Mr. Hoffman and Dr. Reed were involved in sample size considerations for a number of potential projects which may be supported in the future by NICHD. One of the proposed studies concerned dietary interventions in maternal PKU with Dr. Felix de la Cruz of the Mental Retardation and Developmental Disabilities Branch. Similar computations of sample size requirements were provided for a proposed study to identify and treat genito-urinary infections that are suspected to be associated with prematurity. Drs. Duane Alexander, Charlotte Catz, Donald McNellis, and Sumner Yaffee of the Center for Research on Mothers and Children were the NICHD program staff primarily involved in the project development.

Mr. Hoffman and Mrs. Bryla were also involved in providing input to the concept clearance for a proposed study of the long-term developmental sequelae for infants exposed to the chloride-deficient Neo-Mull-Soy formula in infancy. Drs. Berendes, Forman, and Mills, EBRP, were the other participants from the program involved in the development and design of the proposed contract.

Mrs. Bryla and Mr. Hoffman were asked by Ms. Virginia Cain and Dr. Wendy Baldwin, Social and Behavioral Science Branch, CPR, to propose appropriate pre- and postnatal questions for possible inclusion in the National Longitudinal Survey of Labor Force Behavior being supported in part by their branch. Also, Dr. McNellis, CRMC, and Dr. Forman, EBRP, provided major input for the revised pilot questionnaire.

Mr. Hoffman, Mrs. Bryla, and Ms. Carter also were involved in a project to provide statistical summaries for use by Dr. Berendes in his presentation to the next NICHD Council to honor the 20-Year Anniversary of the founding of the Institute. This effort will also result in an NICHD publication

entitled, "NICHD Update: 1962-1982", to provide a public record of the significant trends and developments in the past 20 years in the fields of Maternal and Child Health and Population Research.

Mr. Graubard has also consulted with Ms. Marilyn Rosenstein, Division of Biometry, NIMH, and Dr. Vivian Faden, Statistical and Mathematical Applications Branch, ADMHA, regarding principles of statistical design for surveys and methods of estimation for a variety of institutional and physician-based surveys conducted by NIMH.

Mr. Hoffman and Mr. Graubard have been involved with Dr. Michele Forman in the analysis of data relating to the effects of breast feeding upon the incidence during the first year of life of gastroenteritis and respiratory infections among the Pima/Papago Indian children. They have also participated with Drs. Forman, Berendes, and Naggan in the design and preliminary analysis of data on cultural trends involving breast feeding among the Bedouin Arabs in Israel. Also, Mr. Graubard and Mr. Sahlroot have provided statistical advice to Ms. Natalie Truran and Dr. Forman on the analysis of pilot data from the George Washington University Infant Feeding Survey.

Dr. Reed continues to represent NICHD on the NIH Working Group on the Census-National Death Index Study which is being proposed by the Epidemiology Branch of NHLBI. It is proposed that a sample of respondents to the 1980 Census be matched annually against new deaths as recorded on the National Death Index, recently installed by the National Center for Health Statistics. The purpose is to gain a prospective view of the antecedents of mortality as provided by the census data. The task of the working group is to assess the feasibility of the study via a pilot study and to determine its usefulness to the participating institutes.

Dr. Reed attended the 37th Annual Conference on Applied Statistics in Newark, NJ in December, 1981. Mr. Hoffman attended a Workshop at the Centers for Disease Control, Atlanta, Georgia in August, 1982, to consider the merits of a proposed Study of Multivitamin/Mineral Supplementation as Preventive Measures Against the Occurrence of Neural Tube Defects in the U.S. Population. Mr. Hoffman also attended several meetings of the NIH Clinical Trials Committee, chaired by Dr. Robert Gordon, Office of the Director, NIH, as an alternate for Dr. Berendes during this past year.

EBRP Seminar speakers sponsored by Mr. Hoffman this year included: (1) Dr. Robin Knill-Jones, Department of Community Medicine, University of Glasgow, Scotland, who spoke on "Occupation of Female Doctors and Outcome of Pregnancy" in October, 1981; (2) Dr. Jose Villar, Department of Maternal and Child Health, The Johns Hopkins University, who spoke on "Postnatal Growth Patterns of Infants with In-utero Growth Retardation: Comparison of Findings from the United States and Guatamala" in January, 1982; and (3) Dr. Valerie Dowding, Department of Community Health, Trinity College Medical School, University of Dublin, Ireland, who spoke on "Birth Weight, Social Class and Perinatal Mortality in Dublin." In addition to these speakers, the Biometry Branch was also visited for two days by Dr. Mehari Gebre-Medhin, Department of Pediatrics, University of Uppsala, Sweden, to discuss his recent work in inferring the nutritional status of the mother and fetus based on the analysis of biochemical markers from samples of maternal and cord blood obtained at

the end of pregnancy.

Other activities of the Biometry Branch staff included serving as referees for papers submitted to Science, the American Journal of Clinical Nutrition, American Journal of Epidemiology, and Preventive Medicine - An International Journal. Also, members of the staff served on panels reviewing the responses to Requests for Proposals issued by the NICHD.

The departures from the Biometry Branch of previous members of the staff occasioned the recruitment of three new persons in the past year: Mr. Barry I. Graubard (Mathematical Statistician), Mrs. Mary D. Overpeck (Survey Statistician), and Ms. Dawn T. Beard (Clerk/Typist). Mr. Nirakar C. Saxena, Senior Research Statistician, Indian Council for Medical Research, New Delhi, India, and a WHO Fellow, was a Guest Worker in the Branch through December, 1981. Dr. Olav Meirik, Senior Physician, Department of Obstetrics and Gynecology, Uppsala University, Sweden, joined the staff as a Visiting Scientist for one year beginning in August, 1982. Mr. Richard Staton was on detail to the Biometry Branch from the Intramural Research Program during part of the year. Three graduate students in medicine, biostatistics, and mathematical statistics (Ms. Leigh D. Baker, Ms. Olivia D. Carter, and Mr. Todd Sahlroot, respectively) were employed as summer workers this year.

A summary of publications, talks, research projects and contracts follows.

NICHD Annual Report

October 1, 1981 through September 30, 1982

Biometry Branch

Publications:

Bakketeig, L.S., and Hoffman, H.J.: The tendency to repeat gestational age and birth weight in successive births related to perinatal survival. Acta Obstet. Gynecol. Scand. (In press).

Bakketeig, L.S., Hoffman, H.J., and Oakley, A.J.: The epidemiology of perinatal mortality. In Bracken, M.B. (Ed.): Perinatal Epidemiology. New York, N.Y., Oxford University Press (In press).

Brittain, E., Schlesselman, J.J., and Stadel, B.V.: Costs of case-control studies. Am. J. Epidemiol. 114:234-43, 1981.

Denman, D.W., and Schlesselman J.J.: Interval estimation of the attributable risk for multiple exposure levels in case-control studies. Biometrics (In press).

Eckardt, M.J., Ryback, R.S., Rawlings, R.R., and Graubard, B.I.: A reply to the letter entitled: Selection of controls in testing for alcoholism. J. Am. Med. Assoc. 247:2497, 1982.

Eckardt, M.J., Graubard, B.I., Ryback, R.S., and Gottschalk, L.A.: Pre-treatment consumption as a predictor of post treatment consumption in male alcoholics. Psychiatry Research (In press).

Eckardt, M.J., Ryback, R.S., Rawlings, R.R., and Graubard B.I.: Biochemical diagnosis of alcoholism - A test of the discriminating capabilities of - Glutamyl transpeptidase and mean corpuscular volume. J. Am. Med. Assoc. 246:2707-2710, 1981.

Forman, M.R., Hoffman, H.J., Harley, E.E., Cross, J., and Bennett, P.: The PIMA infant feeding study: The role of sociodemographic factors in the trend in breast and bottle feeding. J. Clin. Nutrition 35:1477-1486, 1982.

Harper, R.M., Leake, B., Hoffman, H.J., Walter D.O., Hoppenbrouwers, T., Hodgman, J., and Sterman, M.B.: Periodicity of sleep states is altered in infants at risk for the Sudden Infant Death Syndrome. Science 213:1030-1032, 1981.

Hillman, L., Hoffman, H.J., Jones, M., Van Belle, G., Goldberg, J., Kraus, J.F., Peterson, D.R., Pakter, J., Janerich, D.T., Damus, K., and Hasselmeier, E.G.: Relationship of prenatal and neonatal factors to SIDS: Preliminary results of the NICHD Cooperative Epidemiological Study of Sudden Infant Death Syndrome (SIDS) Risk Factors. (Abstract) J. Pediatric Research 16:291, 1982.

Hoffman, H.J., and Bakketeig, L.S.: The classification of birth weight and prematurity. In Bracken, M.B. (Ed.): Perinatal Epidemiology. New York, N.Y., Oxford University Press (In press).

Hoffman, H.J., and Bakketeig, L.S.: Fetal and perinatal mortality comparisons between the United States and Norway. Int. J. Gynecology & Obstetrics (In press).

Hoffman, H.J., Hunter, J., and Hasselmeyer, E.G.: S.I.D.S. and D.P.T. In Hinman, A.R. (Ed.): Proceedings of the 17th Immunization Conference. Atlanta, Ga., Centers for Disease Control, 1982.

Rawlings, R.R., Rae, D.S., Graubard, B.I., Eckardt, M.J., and Ryback, R.S.: A methodology for construction of a multivariate diagnostic instrument: An application to alcohol abuse screening. Computers in Biomedical Research 15:228-239, 1982.

Reppert, S.M., Perlow, M.J., Ungerleider, L., Mishkin, M., Tamarkin, L., Orloff, D.G., Hoffman, H.J., and Klein, D.C.: Effects of damage to the suprachiasmatic area of the anterior hypothalamus on the daily melatonin and cortisol rhythms in the Rhesus monkey. J. Neurosciences 1:1414-1425, 1981.

Schlesselman, J.J.: Case-Control Studies: Design, Conduct, Analysis. New York, N.Y., Oxford University Press, 1981, 354 pp.

Smith, H.J., Newman, J.D., Hoffman, H.J., and Fetterly, K.: Statistical discrimination between vocalizations of individual squirrel monkeys. Folio Primatologia 37:267-279, 1982.

Steinherz, R., Reed, G.F., and Schulman, J.D.: HLA types and the clinical course of cystinosis. Israel Journal of Medical Sciences 18:293, 1982.

Talks:

Hoffman, H.J.: Design of the study. Symposium on the NICHD Cooperative Epidemiological Study of Sudden Infant Death Syndrome (SIDS) Risk Factors. Annual Meeting of the American Pediatric Society - Society for Pediatric Research. Washington, D.C., May, 1982.

Hoffman, H.J.: SIDS and DPT. The 17th Immunization Conference at the Centers for Disease Control. Atlanta, Georgia, May, 1982.

Hoffman, H.J.: Epidemiology of adverse outcomes of pregnancy. Invited presentation for an interdisciplinary conference on "Exposure Assessment: Problems and Prospects". National Institutes of Health, Bethesda, Md., September, 1982.

Rawlings, R.R., Graubard, B.I., Rae, D.S., Eckardt, M.J., and Ryback, R.: A comparison of discriminate functions where each population is a mixture of normals. The Annual Meeting of the American Statistical Association. Cincinnati, Ohio, August, 1982.

Reed, G.F.: Estimating withdrawal periods using animal drug depletion data. The Annual Meeting of the American Statistical Association. Cincinnati, Ohio, August, 1982.

Ryback, R., Eckardt, M.J., Negron, G., Rawlings, R.R., Cornas, R.C., Chobanian, S., and Graubard, B.I.: Clinical and chemical correlates of alcoholism in alcoholic and non alcoholic women. Invited presentation for the National Council on Alcoholism, April, 1982.

Ryback, R., Eckardt, M.J., Negron, G., Rawlings, R.R., Chobanian, S., and Graubard, B.I.: Biochemical correlates of alcoholism: A replication in progress. An invited presentation at the Annual Meeting of the American Psychiatric Association, May, 1982.

Spiliotis, B., Lee, B.C., Pineda, J., Denman, D.W., Hoffman, H.J., Brown, T., and Bercu, B.B.: Time series analysis of pulsatile gonadotropin and testosterone secretion during sexual development in the male macaque. The Endocrine Society Annual Meeting, San Francisco, California, June, 1982.

1982 Annual Report
Biometry Branch

<u>Project Numbers</u>	<u>Project Title</u>	<u>Principal Investigator</u>
Z01-HD-00801-07 BB	Studies based on the Medical Birth Registries of Norway (1967-1973) and Sweden (1977-1981).....	H. Hoffman
Z01-HD-00802-07 BB	Study of Linked Information on Infant Death Certificates and Live Birth Certificates for Selected U.S. States.....	H. Hoffman
Z01-HD-00860-02 BB	Analysis of Biomedical Time Series Data.....	H. Hoffman
Z01-HD-00818-01 BB	Research in Developing Nonparametric Methods for Biomedical Applications.....	G. Reed
Z01-HD-00811-03 BB	National Collaborative Cysteamine Study Data Center.....	G. Reed
Z01-HD-00813-01 BB	Methodology for Laboratory Animal Research, including Bio-assay, Life Tables, and Dose-Response Studies.....	G. Reed
Z01-HD-00820-01 BB	Statistical methods for Epidemiologic Data.....	D. Denman
Z01-HD-00830-01 BB	Child Health Supplement to the 1981 NCHS Health Interview Survey..	M. Overpeck
Z01-HD-00840-01 BB	Statistical Discriminate Methods with Applications to Alcoholism Screening.....	B. Graubard
Z01-HD-00841-01 BB	Methods for Comparing and Analyzing Data from Several Complex Surveys.....	B. Graubard
Z01-HD-00850-06 BB	Randomized, Controlled Study of Phototherapy for Neonatal Hyperbilirubinemia.....	D. Bryla
Z01-HD-00851-01 BB	Trends in Time Relating to Maternal and Child Health and Population Research.....	D. Bryla

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00801-07
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PERIOD COVERED
October 1, 1981, to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Studies based on the Medical Birth Registries of Norway (1967-1973) and Sweden (1977-1981)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator:
Howard J. Hoffman Chief BB NICHD

Other Investigators:

Olav Meirik	Visiting Scientist	BB	NICHD
Heinz W. Berendes	Director	EBRP	NICHD
Ernest Harley	Supervisory Computer Spec.	EBRP	NICHD
Karen Fetterly	Computer Specialist	EBRP	NICHD
May Chiu	Computer Specialist	EBRP	NICHD

COOPERATING UNITS (if any) Institute of Hygiene and Social Medicine, University of Bergen, Norway, Department of Community Medicine, Univ. of Trondheim, Norway, Departments of Obstetrics & Gynecology and Social Medicine, Univ. of Uppsala, and Department of Social Affairs, Stockholm, Sweden

LAB/BRANCH
Biometry Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: .7	PROFESSIONAL: .5	OTHER: .2
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

These studies have focused on: (1) the relation of the quality of medical care to the risk of perinatal death in Norway and Sweden, (2) the tendency to repeat similar birth weight and gestational age in subsequent pregnancy outcomes to the same mothers, (3) perinatal mortality in relation to order of birth and size of sibship, (4) epidemiologic risk factors for preterm birth, and (5) epidemiologic risk factors for small-for-gestational age births.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00802-07
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PERIOD COVERED
October 1, 1981, to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Study of Linked Information on Infant Death Certificates and Live Birth Certificates for Selected U.S. States

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator:
Howard J. Hoffman Chief BB NICHD

Other Investigators:

Dolores A. Bryla	Statistician	BB	NICHD
Mary D. Overpeck	Survey Statistician	BB	NICHD
Olav Meirik	Visiting Scientist	BB	NICHD
Heinz W. Berendes	Director	EBRP	NICHD
Samuel Kessel	Medical Officer	EBRP	NICHD
Ernest Harley	Supervisory Computer Spec.	EBRP	NICHD
Karen Fetterly	Computer Specialist	EBRP	NICHD
May Chiu	Computer Specialist	EBRP	NICHD

COOPERATING UNITS (if any)
Departments of Health in the following states: California, Colorado, Illinois, Minnesota, Missouri, New York, (state and city), North Carolina, Rhode Island and Washington

LAB/BRANCH
Biometry Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: .3	OTHER: .7
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objectives are to assemble a multi-state data file of infant deaths in which prior linkage with birth certificate information has been performed. The studies to be done on the data set include associations between infant and fetal mortality with the standard information on birth certificates (e.g. birth weight, gestational age, maternal age and race, parity, etc.). These studies will be compared with similar studies on a 1950 and 1960 cohort of U.S. births. Additional comparisons will be made to linked data from Canada (1971), Great Britain (1970), Norway (1967-1976), and Sweden (1975-1980).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00860-02
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PERIOD COVERED
October 1, 1981, to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Analysis of Biomedical Time Series Data

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator:
Howard J. Hoffman Chief BB NICHD

Other Investigators:
Daniel Denman Mathematical Statistician BB NICHD
Florence Comite Clinical Associate DEB NICHD
Nancy Vieira Biologist NPMB NICHD
Barry Bercu Medical Officer NPMB NICHD

NIA Investigator:
Mary Ann Brock Biologist CP NIA

COOPERATING UNITS (if any) James B. Brown, Professor, Department of Obstetrics and Gynecology, University of Melbourne, Australia. Griff T. Ross, Dean, Univ. of Texas Medical School at Houston. James W. Hansen, Associate Director, Pediatric Nutrition, Mead Johnson Company.

LAB/BRANCH
Biometry Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: 0.75	PROFESSIONAL: 0.50	OTHER: .25
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objectives of this project are: (1) To characterize developmental patterns from daily measurements of gonadotropins and for estrogens in premenarchial girls and pubescent boys based on radioimmuno assay methods for measuring urinary luteinizing hormone, urinary follicle stimulating hormone, and urinary estradiol, estriol and estrone hormones, (2) gonadotropins in both castrated and intact male monkeys of different ages, and (3) growth hormone in normal and precocious pubertal children. (4) To assess circadian and other rhythms in heart rate, temperature and other serial data collected from long-term studies in humans, (5) To perform analysis of these serial measurements using methods of statistical time series analysis, including autoregressive filtering, auto- and cross-spectrum analysis, and robust smoothing procedures.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00818-01
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PERIOD COVERED
October 1, 1981, to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Research in Developing Nonparametric Methods for Biomedical Applications

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator:
George F. Reed Mathematical Statistician BB NICHD

Other Investigators:
Daniel Denman Mathematical Statistician BB NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Biometry Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: .1	PROFESSIONAL: 0.1	OTHER: .0
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective is to investigate and develop distribution-free methods in areas of application for which standard parametric techniques are inappropriate or too sensitive to violations of underlying assumptions.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00811-03
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PERIOD COVERED
October 1, 1981, to September 30, 1982

TITLE OF PROJECT (80 characters or less)

National Collaborative Cysteamine Study Data Center

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator:
George F. Reed Mathematical Statistician BB NICHD

Other Investigators:
Daniel Denman Mathematical Statistician BB NICHD
Ernest Harley Supervisory Computer Spec. EBRP NICHD
Elva Nelson Statistical Assistant EBRP NICHD
Joseph Schulman Chief HBDG NICHD

COOPERATING UNITS (if any)

Jerry Schneider Univ. California, San Diego School of Medicine	James J. Schlesselman Uniform Services Univ. of the Health Sciences	Jess Thoene Univ. of Michigan Medical School
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LAB/BRANCH
Biometry Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.00	.5

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study is a clinical trial to determine the safety and efficacy of cysteamine in the treatment of nephropathic cystinosis, a metabolic disease which usually leads to end-stage renal disease before 10 years of age. All children enrolled in the trial will receive cysteamine. Control information is provided by data collected on 30 patients who were randomized to placebo in a previous trial evaluating the efficacy of Vitamin C for the treatment of this disease. Approximately 60 children will eventually be enrolled in the current trial, which is anticipated to last about three years. Evaluation of the drug's effectiveness will be chiefly determined by the creatinine clearance values of the treated children as compared with those of the historical controls.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00813-01
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PERIOD COVERED
October 1, 1981, to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Methodology for Laboratory Animal Research, including Bioassay, Life Tables, and Dose-Response Studies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator:
George F. Reed Mathematical Statistician BB NICHD

Other Investigators:
Howard J. Hoffman Chief BB NICHD
Olivia D. Carter Mathematical Statistician BB NICHD
Donald Mattison Medical Officer. PR NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Biometry Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: .30	PROFESSIONAL: .20	OTHER: .10
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Research in the variety of design and analysis problems arising from animal studies for (1) evincing dose-response relationships, (2) bioassay and potency estimation, (3) time to event, life table analyses, and (4) other investigations of external stimuli effects with animal models.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00820-01
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PERIOD COVERED
October 1, 1981, to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Statistical Methods for Epidemiologic Data

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator:
Daniel Denman Mathematical Statistician BB NICHD

Other Investigators:

Howard J. Hoffman	Chief	BB	NICHD
Barry I. Graubard	Mathematical Statistician	BB	NICHD
George F. Reed	Mathematical Statistician	BB	NICHD
Olav Meirik	Visiting Scientist	BB	NICHD
Nirakar C. Saxena	Guest Worker	BB	NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Biometry Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.80	0.80	0.00

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to develop and evaluate statistical methods appropriate to data arising in epidemiologic research. Both theoretical research and computer applications are included.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00830-01
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PERIOD COVERED
October 1, 1981, to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Child Health Supplement to the 1981 NCHS Health Interview Survey

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator:
Mary D. Overpeck Survey Statistician BB NICHD

Other Investigators:

Howard J. Hoffman	Chief	BB	NICHD
Dolores A. Bryla	Statistician	BB	NICHD
Leigh D. Baker	Biologist (Summer)	BB	NICHD
Barry I. Graubard	Mathematical Statistician	BB	NICHD
George F. Reed	Mathematical Statistician	BB	NICHD
Heinz W. Berendes	Director	EBRP	NICHD
Duane Alexander	Medical Officer	EBRP	NICHD

COOPERATING UNITS (if any)
National Center for Health Statistics (NCHS), Division of Health Interview Statistics

LAB/BRANCH
Biometry Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: .80	PROFESSIONAL: .75	OTHER: .05
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project provides data on a nationwide sample of 17,000 children of indices of child development, childhood morbidity, school performance and behavior. It will establish normative ranges for the U.S. as well as determining the long-term consequences of perinatal and early childhood risks. The survey was conducted by the National Center for Health Statistics in collaboration with NICHD and others.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01-HD-00840-01

PERIOD COVERED
October 1, 1981, to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Statistical Discriminate Methods with Applications to Alcoholism Screening

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator:

Barry I. Graubard	Mathematical Statistician	BB	NICHD
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ADMHA Investigators:

Robert R. Rawlings	Chief	SMAB	ADMHA
Donald S. Rae	Mathematician	SMAB	ADMHA
Michael J. Eckardt	Research Psychologist	LCS	NIAAA
Ralph S. Ryback	Medical Officer	LPS	NIAAA

COOPERATING UNITS (if any)
Alcohol Drug Abuse and Mental Health Administration
Dept. Obstetrics & Gynecology
Naval Medical Center Bethesda

LAB/BRANCH
Biometry Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.20	0.20	0.00

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective is to study the statistical properties of a variety of discriminate functions and to determine how well they differentiate between alcoholic, other diseased, and normal populations using standard batteries of blood chemistries. These populations have been mainly male but populations of pregnant and nonpregnant women will soon be tested in a similar way.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00841-01
PERIOD COVERED October 1, 1981, to September 30, 1982		
TITLE OF PROJECT (80 characters or less) Methods for Comparing and Analyzing Data from Several Complex Surveys		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT Principal Investigator: Barry I. Graubard Mathematical Statistician BB NICHD Other Investigators: Howard J. Hoffman Chief BB NICHD Mary D. Overpeck Survey Statistician BB NICHD NCHS Investigators: Robert J. Casady Chief SMS/ORM NCHS Jai Choi Mathematical Statistician SMS/ORM NCHS Mary Grace Kovar Spec. Asst./Statistician OISP NCHS Gail Poe Statistician SPDB NCHS		
COOPERATING UNITS (if any) National Center for Health Statistics		
LAB/BRANCH Biometry Branch		
SECTION		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Md. 20205		
TOTAL MANYEARS: 0.10	PROFESSIONAL: 0.10	OTHER: 0.00
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The objective is to compare available <u>statistical methods</u> for conducting data analysis with <u>complex survey data</u> , using data from the <u>National Natality Follow-back Survey (1981)</u> , the <u>Child Health Supplement to the National Health Interview Survey (1981)</u> and <u>Cycle II of the Family Growth Survey</u> . Also, new methods will be theoretically and empirically investigated.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00850-06
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PERIOD COVERED
October 1, 1981, to September 30, 1982

TITLE OF PROJECT (80 characters or less):
Randomized, Controlled Study of Phototherapy for Neonatal Hyperbilirubinemia

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator:			
Dolores A. Bryla	Statistician	BB	NICHD
Other Investigators:			
Howard J. Hoffman	Chief	BB	NICHD
Karen L. Fetterly	Computer Specialist	EBRP	NICHD
Leigh D. Baker	Biologist (Summer)	BB	NICHD
Project Officer:			
James B. Sidbury	Scientific Director	IRP	NICHD

COOPERATING UNITS (if any) Downstate Medical Center, State Univ., N.Y.
 Albert Einstein College of Medicine Univ. of Southern California
 Long Island Jewish-Hillside Medical Center Medical Center
 Medical College of Virginia Univ. of Cincinnati

LAB/BRANCH
Biometry Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: 1.25	PROFESSIONAL: 1.00	OTHER: .25
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study is a cooperative, randomized clinical trial to determine the safety and efficacy of phototherapy for treatment of neonatal hyperbilirubinemia by comparing phototherapy with non-phototherapy infants under specific conditions. Babies were randomized by weight (less than 2,000, 2,000 - 2,499 and greater than 2,499 grams) to the phototherapy or non-phototherapy groups. Infants 2,000 grams and above were admitted to the study when their bilirubin reached levels specified in the study protocol. All infants under 2,000 grams were admitted. Physical, neurological and mental development of these infants will be followed through six years of age.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00851-01
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PERIOD COVERED
October 1, 1981, to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Trends in Time Relating to Maternal and Child Health and Population Research

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator:
Dolores A. Bryla Statistician BB NICHD

Other Investigators:
Heinz W. Berendes Director EBRP NICHD
Howard J. Hoffman Chief BB NICHD
Olivia D. Carter Mathematical Statistician BB NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Biometry Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: 0.15	PROFESSIONAL: 0.10	OTHER: 0.05
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This objectives of this project are (1) to develop time trends relating to maternal and child health and populations research, (2) illustrate the time trends appropriately, (3) publish the data, and (4) update the data periodically.

NICHD Annual Report
October 1, 1981 through September 30, 1982
Biometry Branch
Epidemiology and Biometry Research Program

Contract Number: Y01-HD-81036

Contract Title: 1980 National Natality Survey (NNS) and 1980 National Fetal Mortality Survey (NFMS)

Contractor: Natality Statistics Branch, National Center for Health Statistics, Hyattsville, Maryland

Money Allocated: \$30,000 (Oct. 1, 1981 - March 31, 1983)

Objectives: The 1980 National Natality and Fetal Mortality Follow-Back Surveys consist of mailed questionnaires sent to mothers, physicians and hospitals for a sample of legitimate births in the U.S. during calendar year 1980. The Fetal Mortality Survey is a 1 in 4 sample of all stillbirths over 20 weeks of gestation and the Natality Survey is a 1 in 500 sample of births. The sample consists of 10,900 live births and 8,000 fetal deaths. Previous follow-back surveys of live births were done in 1963, 1964-66, 1967-69, and 1972. No previous national follow-back survey of fetal deaths has ever been accomplished. The data collected are extensive and include sociodemographic information, pregnancy history, contraception prior to conception, wantedness of the birth, information regarding prenatal care, the delivery episode, breast feeding, exposure to radiation, and use of drugs and smoking during pregnancy. These data will be analyzed in collaboration with several agencies within DHHS and outside investigators. Comparisons will be made where possible to previous surveys or comparable information.

Findings: Data will become available in FY 83 for extensive analysis. Public use tapes are being prepared by NCHS and will also be released in FY 83. To date, only very preliminary tabulations have been run. This year's effort has been spent largely on cleaning and editing the data and preparation of the preliminary data tapes.

Significance: These data are of potential interest to several of the program areas and researchers within the Institute. The interests of several staff members from CPR, CRMC and EBRP have been identified and shared with the NCHS personnel who will be coordinating the initial phase of the research activities based on these data tapes.

Proposed Course: This project began with joint sponsorship by EBRP and CRMC in 1977. Many of the original questions were first drafted by the two original NICHD project officers, Richard Stark, M.D. and Michele Forman, Ph.D., with additional assistance from other NICHD staff. In the current year, support for this project has also come from CPR based on the type of data which will be available for analysis. In the coming year, the Institute will have the first data tape to begin analyzing information from this project.

Project Officers: Howard J. Hoffman, M.A., Michele R. Forman, Ph.D., Jeffrey Evans, Ph.D., and Donald McNellis, M.D.

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Epidemiology Branch EBRP/NICHD

During the past year the following changes occurred in the Branch staff: active recruitment for the position of Branch Chief was carried out and Dr. George Rhoads was selected and will assume the position in early September 1982, and Ms. Natalie Truran was brought on as a Research Assistant. Mr. Nugent completed the period of additional training at John Hopkins University to which he has been assigned for the past two years. The professional full-time staff of the Branch currently consists of Dr. Forman and Mr. Nugent.

Projects in which members of the Branch have or have had primary responsibility during the past year include:

1. The Seasonality of Infant Mortality from Linked Birth-Death Records in Minnesota, 1967-73.
2. Infant Feeding Among The Pima Indians: Time-Trend Factors Associated with Infant Feeding and Its Effect on Child Health.
3. The Epidemiology of Infant Mortality in Baltimore, MD.
4. The Effects of Exposure to Westernization on Infant Feeding Patterns Among the Negev Bedouins.
5. The Relationship of Body Density to Other Methods of Assessing Obesity In Eight Year Old Children and the Association of Obesity with Present and Past Nutritional and Activity Factors and Parental Attitudes.
6. Breast and Bottle Feeding in the United States: The 1979-80 National Natality Survey.
7. A Prospective Study of the Frequency and Duration of Infant Feeding Practices.

A brief description of these projects is included in the next section.

Additional areas of concern of the Branch staff include the effects of delayed child-bearing and ascertaining the role of cervical infections during pregnancy in increasing the risk of premature delivery. Additional contract requests are being developed in these areas.

Other professional activities of the staff included presentations at the University of Maryland and at national meetings. Staff members have also been involved in several committees of national significance such as the DHHS Infant Feeding Task Force on which Dr. Forman participated as a review member. Dr. Forman has also been involved as a member of the Review Panel of the Four Country Infant Feeding Study sponsored by the Department of State's Agency for International Development. Dr. Forman also presented a paper at the American Anthropology Association meeting, December 1981, in Los Angeles, California, entitled "The Pima Infant Feeding Study: The Role of Sociodemographic and Attitudinal Factors in the Trend in Breast and Bottle Feeding." Mr. Nugent was a co-author of a paper presented at the Society for Epidemiologic Research meeting, June 1982, in Cincinnati, Ohio, entitled "Seasonality of Perinatal Mortality and Preterm Delivery in Minnesota 1967-73."

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00310-05 EB/Inter- agency Clinical Investig. No.78-CH-102 w/NIAMDD
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PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Infant Feeding Among the Pima Indians: Time-Trend Factors Associated With
Infant Feeding and Its Effect on Child Health.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER
PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	:	Michele R. Forman	Epidemiologist	EB/EBRP/NICHD
Others	:	Ernest Harley	Computer Specialist	CS/EBRP/NICHD
		Peter Bennett	Chief	EFB/NIAMDD
		Robert Beren	Med. Records Abstract.	EB/EBRP/NICHD
		Howard Hoffman	Biostatistician	BB/EBRP/NICHD
		Barry Graubard	Biostatistician	BB/EBRP/NICHD

COOPERATING UNITS (if any)
NIAMDD

LAB/BRANCH
Epidemiology Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: .95	OTHER: .05
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The decrease in breast feeding among infants in the U.S. from 1940 to 1975 has been reflected in Native American populations in a shorter period of time. This study described changes in breast feeding among the Pima Indians living on a reservation in Arizona and compared the health effects of breast and bottle fed infants over the past 20 years. The availability of centralized health records at the Sacaton Hospital of the Indian Health Service and the relative lack of mobility of the population made this an excellent source for a study of this issue of current national concern.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00311-03 EB
PERIOD COVERED October 1, 1981 through September 30, 1982		
TITLE OF PROJECT (80 characters or less) Breast and Bottle Feeding In The United States: The 1979-80 National Natality Survey		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I. : Michele R. Forman Epidemiologist EB/EBRP/NICHD Others : Ernest Harley Computer Specialist CS/EBRP/NICHD		
COOPERATING UNITS (if any)		
LAB/BRANCH Epidemiology Branch		
SECTION		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205		
TOTAL MANYEARS: .01	PROFESSIONAL: .01	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Participation in the National Natalty Survey of the NCHS will provide data on <u>current breast feeding practices</u> in all segments of the population. Comparison with data from the 1969 Survey will provide data for the assessment of <u>changes in breast and bottle feeding</u> over the last decade.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00318-02 EB																								
PERIOD COVERED October 1, 1981 through September 30, 1982																										
TITLE OF PROJECT (80 characters or less) A Prospective Study of the Frequency and Duration of Infant Feeding Practices																										
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0"> <tr> <td>P.I. :</td> <td>Michele R. Forman</td> <td>Epidemiologist</td> <td>EB/EBRP/NICHD</td> </tr> <tr> <td>Others :</td> <td>Natalie Truran</td> <td>Research Assistant</td> <td>EB/EBRP/NICHD</td> </tr> <tr> <td></td> <td>Ernest Harley</td> <td>Computer Specialist</td> <td>CS/EBRP/NICHD</td> </tr> <tr> <td></td> <td>Howard Hoffman</td> <td>Math. Statistician</td> <td>BB/EBRP/NICHD</td> </tr> <tr> <td></td> <td>Allan Weingold</td> <td>Professor</td> <td>George Wash. Univ.</td> </tr> <tr> <td></td> <td>Judith Gussler</td> <td>Anthropologist</td> <td>Ross Labs.</td> </tr> </table>			P.I. :	Michele R. Forman	Epidemiologist	EB/EBRP/NICHD	Others :	Natalie Truran	Research Assistant	EB/EBRP/NICHD		Ernest Harley	Computer Specialist	CS/EBRP/NICHD		Howard Hoffman	Math. Statistician	BB/EBRP/NICHD		Allan Weingold	Professor	George Wash. Univ.		Judith Gussler	Anthropologist	Ross Labs.
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	Allan Weingold	Professor	George Wash. Univ.																							
	Judith Gussler	Anthropologist	Ross Labs.																							
COOPERATING UNITS (if any) George Washington University Medical Center																										
LAB/BRANCH Epidemiology Branch																										
SECTION																										
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205																										
TOTAL MANYEARS: 1.0	PROFESSIONAL: .60	OTHER: .40																								
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input checked="" type="checkbox"/> (a2) INTERVIEWS																										
SUMMARY OF WORK (200 words or less - underline keywords) <p>Statements like "<u>my milk dried up</u>" and "<u>I had too little milk</u>" are frequent reasons why women stop breast feeding before six months. Since breast feeding has been the norm for infant feeding for centuries, it would seem that <u>milk insufficiency</u> may be less of a physiological inability and more of a socio-cultural condition. Thus it is the objective of this study to examine the role of <u>psychosocial</u> as well as <u>physiological</u> factors in the termination of breast feeding.</p>																										

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00306-05 EB												
PERIOD COVERED <p style="text-align: center;">October 1, 1981 through September 30, 1982</p>														
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;">The Seasonality of Infant Mortality from Linked Birth-Death Records in Minnesota, 1967-73</p>														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width:100%; border: none;"> <tr> <td style="width:30%;">P.I. :</td> <td style="width:30%;">Robert P. Nugent</td> <td style="width:30%;">Epidemiologist</td> <td style="width:10%;">EB/EBRP/NICHD</td> </tr> <tr> <td>Others :</td> <td>Carl A. Keller</td> <td>Epidemiologist</td> <td>NIEHS</td> </tr> <tr> <td></td> <td>Karen Fetterly</td> <td>Computer Specialist</td> <td>CS/EBRP/NICHD</td> </tr> </table>			P.I. :	Robert P. Nugent	Epidemiologist	EB/EBRP/NICHD	Others :	Carl A. Keller	Epidemiologist	NIEHS		Karen Fetterly	Computer Specialist	CS/EBRP/NICHD
P.I. :	Robert P. Nugent	Epidemiologist	EB/EBRP/NICHD											
Others :	Carl A. Keller	Epidemiologist	NIEHS											
	Karen Fetterly	Computer Specialist	CS/EBRP/NICHD											
COOPERATING UNITS (if any)														
LAB/BRANCH <p style="text-align: center;">Epidemiology Branch</p>														
SECTION														
INSTITUTE AND LOCATION <p style="text-align: center;">NICHD, NIH, Bethesda, MD 20205</p>														
TOTAL MANYEARS: <p style="text-align: center;">.67</p>	PROFESSIONAL: <p style="text-align: center;">.67</p>	OTHER:												
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS														
SUMMARY OF WORK (200 words or less - underline keywords) <p>The observed <u>seasonality of neonatal deaths</u> in the U.S. has implications as to the role of <u>environmental agents</u>, e.g., infectious organisms, during pregnancy in influencing pregnancy outcomes. Since <u>seasonality of conceptions</u> may generate seasonality of neonatal death rates, <u>linked birth-death records from Minnesota</u> are being utilized to examine this relationship to that seasonality of death rates can be assessed independently of any seasonal variation in conceptions.</p>														

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00324-01 EB
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PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Epidemiology of Infant Mortality in Baltimore, MD

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	:	Robert P. Nugent	Epidemiologist	EB/EBRP/NICHD
Others	:	Carl A. Keller	Epidemiologist	NIEHS
		Michele R. Forman	Epidemiologist	EB/EBRP/NICHD
		Karen Fetterly	Computer Specialist	CS/EBRP/NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Epidemiology Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.5	OTHER:
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A case-control study of all infant deaths occurring in Baltimore, MD, from November 1978-August 1979 was carried out to identify risk factors for infant mortality in a high risk metropolitan area. A total of 182 deaths occurred with complete information on 143 of the cases. Initial analysis of the data obtained is nearing completion. In addition, analysis of linked infant birth and death records for the city of Baltimore is also being conducted.

NICHD ANNUAL REPORT

October 1, 1981 through September 30, 1982

Epidemiology Branch
Contract and Collaborative Research

Contract Title: The Effect of Exposure to Westernization on Infant Feeding Patterns Among the Negev Bedouins

Contractor: Epidemiology and Health Services Evaluation Unit, Center for Health Sciences, Ben Gurion University on the Negev, Beer' Sheva, Israel

Money Allocated: \$290,659.00

Objectives:

1. To document the present trend of infant feeding practices (breast and bottle feeding) among the three groups of Negev Bedouins: The semi-nomadic, the transitional, and the sedentary. This will be achieved by a cross sectional study, interviewing a stratified sample of 900 women who gave birth 5 to 8 months prior to the interview.
2. To describe in this cohort a set of characteristics distinguishing breast from bottle feeders in each of the three groups. To identify factors which influence women to choose to breast feed or bottle feed and determine whether these factors are indicative of exposure to "westernization."
3. To further use the information from this cohort of 900 women to describe whether Bedouin women have changed their infant feeding practices in the last few years, by getting information about older children, born earlier in calendar time to these same women.
4. To prospectively compare whether attitudinal statements of the Bedouin women after delivery, and past behavior (with regard to infant feeding practices of older children), correlate with their behavior 5 to 8 months later. This will be done by consecutive interviews of 1,500 mothers after delivery in the hospital and a second interview 5 to 8 months later.
5. To determine whether breast fed children in the prospective cohort have fewer hospital admissions and shorter average duration of hospital stay in the first 5 to 8 months of life regardless of category and other indices of westernization.

Findings: During FY 82, questionnaires, interviewer and coder manuals were developed. Four interviewers fluent in Arabic, Hebrew, and English were trained. A pilot study was undertaken with 150 mothers of 5 to 8 month olds and 50 mothers of newborns interviewed. Data analysis of the pilot study have been completed followed by a revision of the questionnaires. The study began in the Fall 1981. A tape of the first set of interviews of

mothers with infants of 6 months of age has arrived at NICHD and analyses of the first cohort are currently underway.

Significance of Biomedical Research and Programs of the Institute: An important part of this study will be identification of factors which influence the breast and bottle rate in a population undergoing rapid social change, where commonly bottle feeding is on the increase. Identification of those factors may provide the opportunity to intervene on these variables and significantly reduce the bottle feeding rate in such high risk populations.

Proposed Course: No additional funding is anticipated. Collaborative analysis, using NIH computing staff and facilities, is expected to continue for three years with interim publication of any significant findings.

Project Officer: Michele R. Forman, Ph.D.

NICHD ANNUAL REPORT

October 1, 1981 through September 30, 1982

Epidemiology Branch
Publications and Presentations

Publications:

Forman, M.R., Hoffman, H.J., Harley, E.E., Cross, J., and Bennett, P.H.:
The Pima Infant Feeding Study: The Role of Sociodemographic Factors in
the Trend in Breast- and Bottle-Feeding. Am. J. Clin. Nutr. 35:1477-
1486, 1982.

Presentations:

Forman, M.R.: The Pima Infant Feeding Study: The Role of Sociodemographic
and Attitudinal Factors in the Trend in Breast and Bottle Feeding. Pre-
sented at the American Anthropology Association meeting, Los Angeles,
California, December, 1981.

Keller, C.A. and Nugent, R.P.: Seasonality of Perinatal Mortality and
Preterm Delivery in Minnesota 1967-73. Presented at the Society for
Epidemiologic Research meeting, Cincinnati, Ohio, June, 1982.

ANNUAL REPORT

October 1, 1981 through September 30, 1982

Computer Science Section EBRP/NICHD

The Computer Sciences Section, the third component of EBRP enhanced its mission by becoming the NICHD's central resource for system analysis, design and data processing expertise, in early 1982. The Section is responsible for : (1) the development and implementation of analysis, statistical procedures, data processing procedures in the areas of Epidemiology and Biometry; (2) development, processing and dissemination of management information in such areas as program planning, financial management and grants and contracts and personnel; and (3) provides technical assistance to the Department as well as the Institute in the development of specifications in the field of automatic data processing.

The Section on Systems Design and Data Processing continued its mission of developing and implementing systems for handling the many studies in the Epidemiology and Biometry Research Program area. System staff members continue to provide technical consultation in the discussion of and to collaborate in the design of studies, questionnaire development, data organization, data collection, and to do preliminary programming to answer initial questions arising from study development.

Support in the form of data base maintenance, tabulations and graphing is being provided for the following ongoing studies:

1. A clinical trial that makes use of phototherapy in the treatment of neonatal hyperbilirubinemia;
2. A study of high infant mortality in a nearby metropolitan area designed to determine the relationship of environmental factors to the cause of death for infants who died in the first year of life;
3. Studies using information from linked birth and death certificates for years 1967 through 1978 for several states in the U.S.;
4. A study to determine obesity in early childhood;
5. A study of the tendency to repeat birth weight and gestational age in successive births;
6. An investigation of crown-heel length in physical growth.
7. Diabetes in early pregnancy;
8. Infant mortality in the District of Columbia; and

9. Safety and efficacy of cysteamine in the treatment of nephropathic cystinosis.

The past year has been especially productive for the Section on Systems Design and Data Processing. A major commitment of systems staff time and effort in technical consultation in the development of questionnaires, data collection, data organization as well as pilot study analysis is being provided for the following new studies:

1. The effects of exposure to westernization on infant feeding patterns among the Negev Bedouins;
2. A prospective study of the frequency and duration of infant feeding practices;
3. Fetal growth study;
4. Acetaminophen use in early pregnancy as a risk for congenital malformations; and
5. The risk of adverse pregnancy outcome following cervicitis during pregnancy.

In addition, the section has provided expertise in the systems analysis, design and programming to manipulate information for financial, personnel planning, grants/contracts and other needs for ADP expertise identified by other managers of the institute. Other consultations on new studies have also been performed.

ANNUAL REPORT

October 1, 1981 to September 30, 1982

LABORATORY OF DEVELOPMENTAL NEUROBIOLOGY, IRP

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

TABLE OF CONTENTS

SUMMARY

PROJECT REPORTS

Z01 HD 00047-13 LDN

Biochemical studies of neuronal and other cell types

Z01 HD 00048-08 LDN

Studies of transcriptional level control of neurobiologic and developmental phenomena

Z01 HD 00053-14 LDN

Information processing in the central auditory system of mammals and birds

Z01 HD 00054-08 LDN

Structural and behavioral analysis of vocal communication in squirrel monkeys

Z01 HD 00056-07 LDN

Regulation of ACTH, Endorphin, and MSH synthesis and secretion

Z01 HD 00057-06 LDN (Incorporated into Proj. No. Z01 HD 00705-01 LDN)

Axonal proteins: Biosynthesis, transport, neuronal cytoskeleton, and secretion

Z01 HD 00058-07 LDN

Biosynthesis and secretion of peptides in the vertebrate nervous system

Z01 HD 00062-06 LDN

Brain mechanisms of vocal production in squirrel monkeys

Z01 HD 00064-06 LDN

Neurobiologic studies of neurons and glia from the mammalian central nervous system in cell cultures

Z01 HD 00089-08 LDN

Pineal-pituitary interactions

Z01 HD 00093-08 LDN

The mechanism of action of nerve growth factor

Z01 HD 00094-12 LDN

Regulation of neuroendocrine metabolism: Circadian, stress, light and drug influences (rat, hamster, rhesus monkey)

Z01 HD 00095-12 LDN

Regulation of neuroendocrine metabolism: Transsynaptic mechanisms in the pineal gland

Z01 HD 00096-12 LDN

Regulation of neuroendocrine metabolism: Intracellular mechanisms

Z01 HD 00097-12 LDN

Regulation of neuroendocrine metabolism: Melatonin physiology (rat, hamster, rhesus monkey)

Z01 HD 00700-05 LDN

Cell interactions in synaptogenesis

Z01 HD 00702-02 LDN

Genetics of primate vocal behavior

Z01 HD 00703-02 LDN

Effect of long chain fatty acids on developing neurons in cell culture

Z01 HD 00704-02 LDN

Physiologic effects of tetanus toxin on nerve cells

Z01 HD 00705-01 LDN

Macromolecules involved in the intracellular and intercellular organization of neurons

NICHO ANNUAL REPORT

Laboratory of Developmental Neurobiology

October 1, 1981 to September 30, 1982

The major concern of this laboratory continues to be the analysis of cellular and molecular mechanisms important for the development of the nervous system. Functional studies of the mature system, particularly peptidergic systems, are important as are behavioral analysis of primate communication. The activities of the laboratory are divided among five sections.

I. Section on Neurobiology

The statistical methods that we have developed for analyzing transmitter release in mammalian central nervous system cell cultures are being used to probe differences between cell types with respect to their transmitter release mechanisms and to demonstrate differences in postsynaptic response mechanism. Combined injections of horseradish peroxidase and fluorescent dyes in recorded cells give increased anatomical resolution for correlative morpho-physiological studies of synaptic mechanisms.

A series of anticonvulsant drugs used to treat major and minor motor seizures produce characteristically different effects on cerebral cortical neurons in cell culture when administered chronically in high therapeutic doses. The major motor drugs (phenytoin, phenobarbital, and carbamazepine) produce the greater general toxicity with phenytoin being the most and carbamazepine the least toxic. The minor motor agents (valproate, diazepam and ethosuximide) produce down regulation of the benzodiazepine receptor with diazepam itself being the most potent. The major motor drugs do not exhibit this property and the commonality of the action within the minor motor group of drugs suggests that the down regulation of the benzodiazepine receptor may be related to the therapeutic mechanism of action of this group of drugs.

Synapse formation and competitive interactions are being investigated in co-cultures involving skeletal muscle ciliary ganglion explants and spinal cord cell cultures. A time dependent decrease in ciliary ganglion to muscle synapses occurs when these cells are co-cultured with ventral spinal cord (but not with dorsal root ganglion) neurons. A more direct physiological and biochemical study of synapse formation has begun using the Campenot chamber, which allows independent examination of neuronal cell bodies and their axonal projections which are involved in synapse formation.

The sensitivity of neuronal development to blockade of electrical activity has an abrupt onset (sensitive period) during the seventh day in culture, corresponding to the day of birth in vivo. Cholinergic neurons, but not neurons synthesizing or taking up gamma-aminobutyric acid (GABA), are affected. The biochemical deficit produced by blockade of electrical activity can be prevented by conditioned medium from active (but probably not from inactive) cultures. This is the first example of the activity dependent release of a neurotrophic agent important for the survival of a specific type of neuron.

Molecular hybridization of polysomal polyadenylated messenger RNAs (mRNAs) of undifferentiated (S) and differentiated (P) NS20Y mouse neuroblastoma cells with their complementary DNAs (cDNAs) had shown that there were approximately 6 high abundance and over 600 low abundance mRNAs which were present uniquely in one of the differentiation steps. Comparison of two-dimensional gels of proteins made by intact S and P cells confirmed the presence of some specifically expressed sequences. The S cell-specific sequences may include mRNAs associated with cell division. The P cell-specific sequences may include mRNAs for neuron-specific functions such as neurite extension, synapse formation, and action potential generation. We have continued to develop the technology for molecular cloning of these S and P cell-specific cDNAs, using recombinant DNA techniques. For pilot studies we have used adult mouse brain polyadenylated mRNAs and have cloned some of these sequences, albeit with low efficiency. At present we are working toward improving this efficiency and preparing to use the stripped (of common sequences) and unstripped S and P cell cDNAs we have ready. Although not immediately useful in our plans, brain clones are being characterized and retained for future use.

II. Section on Functional Neurochemistry

The research goal of this Section continues to be the study of peptides and proteins which are involved in intracellular organization and intercellular communication in the nervous system. The overall approach is cell biological in nature and hence utilizes techniques and concepts from a variety of disciplines (e.g., physiology, biochemistry, anatomy, and immunology).

The major focus has been placed on 3 model (biological) systems: 1) the rat hypothalamo-neurohypophysial system, 2) the toad neurointermediate lobe, and 3) the squid nervous system (i.e., the giant axon and synapse, and optic lobes). Neuropeptides which are derived from three prohormones in these systems are under active study with respect to their biosynthesis, packaging, processing, transport, secretion, regulation, and biological action on target organs and cells. These prohormones include pro-pressophysin which yields vasopressin (AVP), neurophysin, and a 39 amino acid glycopeptide; pro-oxyphysin which yields oxytocin (OT), neurophysin, and another cysteine containing peptide; and pro-opiocortin which yields ACTH, endorphin, MSH, LPH, 16K glycopeptide, etc.

The prohormones for vasopressin (propressophysin) and oxytocin (prooxyphysin) and their associated neurophysins have been identified and characterized. Cyanogen bromide cleavage of these prohormones indicates that the oxytocin is on the N-terminal and neurophysin is near the C-terminal in prooxyphysin; and vasopressin is near the N-terminal, neurophysin is in the middle, and the glycopeptide is near the C-terminal in propressophysin.

A method for preparing a highly purified preparation of neurosecretory vesicles from bovine posterior pituitaries has been developed. The pH of the interior of these secretory vesicles was found to be 5.5, using radioactive methylamine distribution methods. Furthermore, the vesicles were shown to have an internal negative membrane potential. ATP in the presence of Mg^{++} caused a large depolarization of these vesicles, and the presence of permeable

Cl⁻ ions caused them to lyse osmotically. Work now in progress involves the use of these secretory vesicles to study the proteolytic enzymes involved in the conversion of the prohormone and for experiments on the vesicle membrane proteins involved in axonal transport and secretion.

The study of the biosynthesis of ACTH, α -MSH and endorphin in the toad, mouse and rat intermediate lobe has continued. These peptides have been shown to be synthesized from a common, glycoprotein precursor (Mol. Wt. 32,000). Recently, a converting activity for the prohormone has been detected in purified secretory granules fractions from rat anterior, intermediate, and neural lobes, and bovine intermediate and neural lobes. The activity appears to be due to an acid thiol protease. This protease is currently being purified, as well as a variety of different posttranslational processing enzymes. Studies on the turnover and regulation of release of the ACTH, α -MSH and endorphin peptides from the toad neurointermediate lobe have led to the discovery of two pools of peptides that differ in their peptide content (one pool contains α -MSH and ACTH but no endorphin while the other contains all three peptides), turnover and regulation of release. Work is now in progress to determine the cellular mechanisms underlying the selective synthesis and storage of the different hormones in the different pools.

Recent studies on the Ca⁺⁺-activated protease distribution in squid nervous system indicate that the protease is found in cell bodies and axons but not terminals (i.e., optic lobe synaptosomes). A hypothesis for the role of this protease in neuronal development has been proposed.

Studies on the effects of AVP on development in neonatal rats have led to the observation that inappropriate levels of this hormone in pregnancy or immediately post-natally in neonates produce profound changes in the development of kidney and possibly other organs. Mechanisms underlying these changes are currently under study.

A program of monoclonal antibody production and utilization has been initiated. Several very specific monoclonal antibodies have been generated, and their antigens in the nervous system are being studied from a cell biological and developmental perspective.

III. Section on Intermediary Metabolism

Investigators in the Section are interested in the biochemical and physiological actions of nerve growth factor and of other growth factors on neural tissue. Our studies are designed to elucidate the role of such factors in the development and maintenance of the nervous system. We are particularly interested in understanding the molecular mechanism(s) by which such factors act. That is, we hope to define the intracellular mediator which translate the interaction of nerve growth factor with its membrane receptor into the signals recognized by the transcriptional apparatus of the cell.

In both normal sympathetic neurons and the PC12 clone of rat pheochromocytoma, nerve growth factor initiates a chain of biochemical events culminating in the induction of neuron-specific enzymes and the outgrowth of neurites.

Among these biochemical alterations is an increase in the phosphorylation of a specific nuclear protein. One of these proteins, a nuclear nonhistone protein, has been studied extensively. In addition to being a target for the action of nerve growth factor, this protein also exhibits increased phosphorylation when PC12 cells are treated with epidermal growth factor, NECA, and TPA. A similar or identical protein shows increased phosphorylation in C6 glioma cells treated with isoproterenol. Although these several agents have different effects on the cells, they all cause changes in the levels of certain enzymes, and accordingly, in the levels of transcription of the corresponding genes. This suggests that the protein is a component of the transcriptional mechanism of the cell, possibly a subunit of one of the RNA polymerases. This hypothesis is being tested through studies on the protein itself and in experiments using antibodies against the polymerases.

Recently we have discovered a second protein whose phosphorylation is altered by treatment of the cells with nerve growth factor. This material is a soluble protein with a molecular weight of 100,000. It exhibits a decreased phosphorylation when the cells are treated with nerve growth factor and labeled with radioactive inorganic phosphate. Most importantly, this protein also shows decreased labeling when the cells are treated with nerve growth factor, lysed, and a cell-free supernatant is labeled with radioactive ATP. The importance of this observation is that it provides, for the first time, a cell-free system which reflects the action of nerve growth factor. It is a tool, therefore, with which we can search directly for the intracellular "message" generated by nerve growth factor. Our data with this system so far indicate that the "message" is not a soluble second messenger, but rather a covalent or spatial alteration in the kinase phosphorylating the 100,000 molecular weight protein. Our data further suggest that for this change to occur, calcium must be present in the environment of the cells.

Our current studies are designed to explore the details of this cell-free system and to determine the molecular alteration responsible for the decreased phosphorylation. We hope that by understanding the chemistry of the altered phosphorylation we can understand the molecular mechanism by which nerve growth factor acts.

IV. Section on Neuroendocrinology

The Section on Neuroendocrinology continues to conduct multidisciplinary investigations of the melatonin rhythm generating system. Within the past year there have been four projects which have been pursued. First, the purification of N-acetyltransferase has been improved and the product that this procedure now produces is highly pure, representing the most pure preparation of this enzyme which is available now. The use of this preparation will allow a better understanding of the neural control of gene expression and the activity of specific enzymes. Computer assisted image analysis of two-dimensional gel is used to study the neural control over the expression of specific gene products. Within the past year it has been possible to identify a cluster of gene products whose expression appears to be regulated by adrenergic cyclic AMP mechanism.

A second activity has been the investigation of the adrenergic control of the levels of cyclic nucleotides in the pineal gland and the most important discovery in this area has been that both pineal cyclic AMP and pineal cyclic GMP are regulated by both alpha- and beta-adrenergic receptors.

A third area of investigation stemming from the discoveries of alpha- and beta-adrenergic control of cyclic AMP has been the investigation of the role of alpha-adrenergic receptors in the regulation of N-acetyltransferase and melatonin production. These studies have indicated that alpha-adrenergic receptors play an important role in the regulation of melatonin production.

A fourth area of investigation has been the study of the photic and neural regulation of indolamines in the pineal gland. A new technique, high pressure liquid chromatography with electrochemical detection, has been used to measure the amounts of 10 different indolamine derivatives in a single rat or sheep pineal gland. This is the first time this type of analysis have been used experimentally.

V. Section on Brain and Behavior

Occupancy by the Section of new facilities at NIHAC has again been delayed past the end of FY82, primarily by the poor performance of an outside contractor. A new contract was awarded in July, 1982, and there is a reasonable expectancy that this space will be available to us by the end of calendar 1982.

Programs of the Section were removed to borrowed space at NIHAC in March, 1982 (LBEB, NIMH). This limited and temporary arrangement (augmented by an unused and badly deteriorated trailer-type laboratory of NICHD IR) provide barely adequate facilities for our programs. A serious problem exists with respect to proper care of research animals during the cold months, and the urgent need for prompt completion of the new Section laboratory cannot be over-emphasized.

During FY82 significant progress was made in two areas. Our studies of vocal signals used during affiliative behavior in squirrel monkeys expanded. We have been collecting and analyzing data on vocal changes associated with the breeding season, and have described in some detail call types and structural details which appear to signal readiness to breed. Our studies have also progressed to recording the developmental usage of affiliative calls, both between mothers and infants and between infants born into "affiliative networks". New initiatives begun during FY82 include examination of vocalizations during stereotyped display behaviors and a program to define and quantify juvenile social play (Dr. Maxeen Biben who joined our staff in February, 1982, will lead this project). We hope not only to learn about play and its significance in this species, but additionally to develop a useful model of normal CNS development which involves social interaction and does not require extensive training.

Collaborative research with LBEB has been active. New findings have been obtained on the effects of anterior limbic lesions on the isolation call. These early results suggest a reduction in isolation calling following damage in these areas rather than changes in the acoustic structure of isolation calls as seen earlier with striatal and thalamic lesions. New initiatives have been undertaken with respect to the possible role of endogenous opiates in isolation call production. Predictable and reproducible effects of morphine and naloxone injections have been described, utilizing the detailed quantitative techniques for isolation call analysis we have developed.

A significant area of expansion (which is dependent on realization of new laboratory space designed with this in mind) for the Section is to consider other primate models of vocal behavior. In this area the study of natural and laboratory-created hybrid individuals is of special interest, as is the comparative analysis of vocal signals in species with dramatically different social organization (owl monkey).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00047-13 LDN
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PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Biochemical studies of neuronal and other cell types

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.A. Neale	Physiologist	LDN	NICHD
	P.K. Sher	Clinical Associate	LDN	NICHD
	P.G. Nelson	Chief	LDN	NICHD
OTHER:	W.H. Habig	Research Chemist	DBP	BB
	R.E. Study	Staff Fellow	LNP	NINCDS
	B.E. Graubard		BB	NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Developmental Neurobiology

SECTION
Section on Neurobiology

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.7	1.9	1.8

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purposes of this research are the investigation of the biochemical characteristics of developing central nervous system (CNS) cells in dispersed cell cultures, and the use of these cultures and sensitive biochemical tests to assess the toxicity, biochemical characteristics, and mechanisms of action of nervous system active drugs. We have used several in situ assay methods to provide evidence for a hierarchy of toxicity among anticonvulsants used to treat major motor seizures (Phenytoin > Phenobarbital > Carbamazepine) and among those drugs used to treat minor motor seizures (Valproic acid > Diazepam > Ethosuximide). Exposure of cultures to the minor motor anticonvulsants results in a selective depression of benzodiazepine (BDZ) receptor binding, and effect not observed with the major motor anticonvulsants. Studies of cortical and spinal cord cultures exposed chronically to diazepam reveal an apparent concentration related down regulation of the BDZ receptor. Cortical and spinal cultures show two specific BDZ receptor populations.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00048-08 LDN															
PERIOD COVERED October 1, 1981 to September 30, 1982																	
TITLE OF PROJECT (80 characters or less) Studies of transcriptional level control of neurobiologic and developmental phenomena.																	
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0" style="width: 100%;"> <tr> <td style="width: 15%;">PI:</td> <td style="width: 60%;">B.K. Schrier Medical Officer</td> <td style="width: 25%;">LDN, NICHD</td> </tr> <tr> <td>OTHERS:</td> <td>C.H. Letendre Guest Worker</td> <td>NHLBI</td> </tr> <tr> <td></td> <td>P.G. Nelson Chief, LDN, IRP, NICHD</td> <td>LDN, NICHD</td> </tr> <tr> <td></td> <td>D. Warren Biol. Lab. Tech</td> <td>LDN, NICHD</td> </tr> <tr> <td></td> <td>D. Van Patten Biol. Aide</td> <td>LDN, NICHD</td> </tr> </table>			PI:	B.K. Schrier Medical Officer	LDN, NICHD	OTHERS:	C.H. Letendre Guest Worker	NHLBI		P.G. Nelson Chief, LDN, IRP, NICHD	LDN, NICHD		D. Warren Biol. Lab. Tech	LDN, NICHD		D. Van Patten Biol. Aide	LDN, NICHD
PI:	B.K. Schrier Medical Officer	LDN, NICHD															
OTHERS:	C.H. Letendre Guest Worker	NHLBI															
	P.G. Nelson Chief, LDN, IRP, NICHD	LDN, NICHD															
	D. Warren Biol. Lab. Tech	LDN, NICHD															
	D. Van Patten Biol. Aide	LDN, NICHD															
COOPERATING UNITS (if any) P. Ross, Department of Biology, University of Chicago																	
LAB/BRANCH Laboratory of Developmental Neurobiology																	
SECTION Section on Neurobiology																	
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland																	
TOTAL MANYEARS: 1.6	PROFESSIONAL: 0.9	OTHER: 0.7															
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																	
SUMMARY OF WORK (200 words or less - underline keywords) Molecular hybridizations of polysomal poly(A)-containing messenger RNAs (mRNAs) of undifferentiated (S) and differentiated (P) S20Y-mouse neuroblastoma cells with their complementary DNAs (cDNAs) had shown that there were many mRNAs which were uniquely present in one of the differentiation steps. We have continued to develop the technology for molecular cloning of these S and P cell-specific cDNAs, using recombinant DNA techniques. We have used mouse brain poly(A) ⁺ mRNA sequences for pilot studies and have obtained several clones of highly abundant sequences from them. We are presently ready to try cloning of S20Y sequences.																	

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00053-14 LDN
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PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Information processing in the central auditory system of mammals and birds

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. Symmes	Chief, Section on Brain and Behavior	LDN, NICHD
	J.D. Newman	Research Physiologist	LDN, NICHD
	S.Shamma	Guest Investigator	LDN, NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Developmental Neurobiology

SECTION
Section on Brain and Behavior

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .25	PROFESSIONAL: .25	OTHER: 0
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

During FY82 a large library of original electrophysiological data was transferred from storage on PDP-12 formatted disks to DEC 11-23 formatted disks. This operation has preserved the large data base collected in the Section relating to neuronal responses in various brain areas. Early in FY82 a new DEC 11-23 system was acquired and made operational. This on-line system offers many significant advantages over the system it replaces, and brings our in-lab computing capability up to modern standards of speed and flexibility. We have begun new analyses of some data transferred in this way, particularly in relation to the distribution of inhibition in cortical cells and the nature of so-called nonmonotonic tone responsive units. No new electrophysiological results have been obtained, in part due to space renovation and in part due to greater emphasis on collecting and analyzing data related to other projects within the Section.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00054-08 LDN
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PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Structural and behavioral analysis of vocal communication in squirrel monkeys

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J.D. Newman Research Physiologist LDN, NICHD
D. Symmes Chief, Section on Brain and Behavior LDN, NICHD
Maxeen Biben Senior Staff Fellow LDN, NICHD

OTHER: Deborah Bernhards Bio Lab Technician LDN, NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Developmental Neurobiology

SECTION
Section on Brain and Behavior

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.5	OTHER: .5
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is concerned with 1) obtaining a detailed description of vocal behavior of squirrel monkeys, with emphasis on the use of specific call types and vocal exchanges associated with affiliative behavior; 2) analyzing the developmental course of vocal behavior by serial recording during growth of laboratory-reared infants; 3) recording and classifying vocal output during various stereotyped species-typical behavior patterns such as mating, genital display, and juvenile play. Studies begun during the previous year on changes in vocal behavior during estrous cycling have been completed and we are now looking at vocal usage during the birth and early dependency periods in stable social groups. Detailed description of the unusual vocal components of male genital display should be completed within FY82.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00056-07 LDN															
PERIOD COVERED October 1, 1981 to September 30, 1982																	
TITLE OF PROJECT (80 characters or less) Regulation of ACTH, Endorphin, and MSH synthesis, processing and secretion.																	
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT																	
<table style="width:100%; border: none;"> <tr> <td style="width:10%;">PI:</td> <td style="width:30%;">Y.P. Loh</td> <td style="width:40%;">Research Chemist</td> <td style="width:10%;">LDN</td> <td style="width:10%;">NICHD</td> </tr> <tr> <td>OTHER:</td> <td>H. Gainer</td> <td>Chief, Sec. on Functional Neurochemistry</td> <td>LDN</td> <td>NICHD</td> </tr> <tr> <td></td> <td>C. Chang</td> <td>Visiting Fellow</td> <td>LDN</td> <td>NICHD</td> </tr> </table>			PI:	Y.P. Loh	Research Chemist	LDN	NICHD	OTHER:	H. Gainer	Chief, Sec. on Functional Neurochemistry	LDN	NICHD		C. Chang	Visiting Fellow	LDN	NICHD
PI:	Y.P. Loh	Research Chemist	LDN	NICHD													
OTHER:	H. Gainer	Chief, Sec. on Functional Neurochemistry	LDN	NICHD													
	C. Chang	Visiting Fellow	LDN	NICHD													
COOPERATING UNITS (if any) T. O'Donohue, Lab. of Clinical Science, NIMH																	
LAB/BRANCH Laboratory of Developmental Neurobiology																	
SECTION Section on Functional Neurochemistry																	
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland																	
TOTAL MANYEARS: 1.3	PROFESSIONAL: 0.8	OTHER: 0.5															
CHECK APPROPRIATE BOX(ES)																	
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER																	
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																	
SUMMARY OF WORK (200 words or less - underline keywords)																	
<p>The biosynthesis of <u>pro-opiocortin</u> has been further studied with an emphasis on <u>post-translational processing mechanisms</u>. A <u>pro-opiocortin converting enzyme</u> activity has been detected in <u>secretory vesicles</u> from anterior, intermediate, and posterior <u>pituitary lobes</u> and partially characterized. The role of <u>glycosylation</u> in <u>lysosomal enzyme routing</u> has also been studied. An acidic <u>acetyltransferase</u> which can acetylate MSH has also been detected in secretory vesicles.</p>																	

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00057-06 LDN
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) Axonal proteins: Biosynthesis, transport, neuronal cytoskeleton, and secretion.		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: H. Gainer Chief, Sec. on Functional Neurochemistry LDN NICHD		
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Developmental Neurobiology		
SECTION Section on Functional Neurochemistry		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) This project has been incorporated into Project No. Z01 HD 00705-01 LDN		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00058-07 LDN																									
PERIOD COVERED October 1, 1981 to September 30, 1982																											
TITLE OF PROJECT (80 characters or less) Biosynthesis, transport, secretion, and biological activity of peptides in the vertebrate nervous system.																											
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT																											
<table style="width:100%; border: none;"> <tr> <td style="width:10%;">PI:</td> <td style="width:40%;">H. Gainer</td> <td style="width:40%;">Chief, Sec. on Func. Neurochemistry</td> <td style="width:10%;">LDN</td> <td style="width:10%;">NICHD</td> </tr> <tr> <td>OTHERS:</td> <td>J. T. Russell</td> <td>Senior Staff Fellow</td> <td>LDN</td> <td>NICHD</td> </tr> <tr> <td></td> <td>Y. Ben-Barak</td> <td>Guest Worker</td> <td>LDN</td> <td>NICHD</td> </tr> <tr> <td></td> <td>M. Whitnall</td> <td>Guest Worker</td> <td>LDN</td> <td>NICHD</td> </tr> <tr> <td></td> <td>G. Handelmann</td> <td>Guest Worker</td> <td></td> <td>NIMH</td> </tr> </table>			PI:	H. Gainer	Chief, Sec. on Func. Neurochemistry	LDN	NICHD	OTHERS:	J. T. Russell	Senior Staff Fellow	LDN	NICHD		Y. Ben-Barak	Guest Worker	LDN	NICHD		M. Whitnall	Guest Worker	LDN	NICHD		G. Handelmann	Guest Worker		NIMH
PI:	H. Gainer	Chief, Sec. on Func. Neurochemistry	LDN	NICHD																							
OTHERS:	J. T. Russell	Senior Staff Fellow	LDN	NICHD																							
	Y. Ben-Barak	Guest Worker	LDN	NICHD																							
	M. Whitnall	Guest Worker	LDN	NICHD																							
	G. Handelmann	Guest Worker		NIMH																							
COOPERATING UNITS (if any) M. Brownstein, Laboratory of Clinical Science, NIMH K. Ozato, PR, NICHD																											
LAB/BRANCH Laboratory of Developmental Neurobiology																											
SECTION Section on Functional Neurochemistry																											
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland																											
TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.0	OTHER: 0.5																									
CHECK APPROPRIATE BOX(ES)																											
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER																											
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																											
SUMMARY OF WORK (200 words or less - underline keywords)																											
<p>The order of peptide components in <u>pro-pressophysin</u> and <u>pro-oxyphysin</u> synthesized <u>in vivo</u> has been found to be <u>AVP-Np-glycopeptide</u> and <u>OT-Np-peptide</u> respectively. The organization of the <u>neurosecretory vesicle</u> has been studied, and shown to have an internal pH of 5.5 produced by a <u>proton-pump ATPase</u> in its membrane. Sixteen <u>monoclonal antibodies</u> specific to the <u>hypothalamo-neurohypophysial</u> system of the rat have been developed, and are under study. A dramatic effect of <u>AVP</u> on <u>kidney development</u> has been demonstrated.</p>																											

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00062-06 LDN
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PERIOD COVERED
Oct. 1, 1981 to Sept. 30, 1982

TITLE OF PROJECT (80 characters or less)
Brain mechanisms of vocal production in squirrel monkeys

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.D. Newman	Research Physiologist	LDN	NICHD
	P.D. MacLean	Chief	LBEB	NIMH
OTHER:	D. Symmes	Head, Section on Brain and Behavior	LDN	NICHD
	M. Murphy	Guest Investigator	LBEB	NIMH

COOPERATING UNITS (if any)
P.D. MacLean and M. Murphy, LBEB, NIMH

LAB/BRANCH
Laboratory of Developmental Neurobiology

SECTION
Section on Brain and Behavior

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 0.5	OTHER: 0.5
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The current phase of this project involves continuing studies on the effects of selective brain lesions on production of the isolation call. Since lesions in the thalamus and midbrain that disrupt production of this vocalization also may encompass fibers arising from more rostral structures, it is important to determine the effects on the isolation call of damage to these rostral structures, particularly the anterior limbic cortex. Ablation of the major extent of the anterior limbic cortex in one subject resulted in failure to produce spontaneous isolation calls over 20 postoperative weeks. A second monkey with a less extensive lesion regained the ability to vocalize after the first postoperative week. The study of the role of opiates and opiate antagonists on Isolation Peep production showed in four subjects a naloxone-reversible reduction or elimination of isolation calls following morphine injections, suggesting that an opiate-dependent mechanism underlies production of this vocalization.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00064-06 LDN
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PERIOD COVERED ~~October~~ 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Neurobiologic studies of neurons and glia from the mammalian central nervous system in cell cultures.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	P. G. Nelson	Chief, Lab. of Dev. Neurobiol.	LDN NICHD
	E.A. Neale	Research Physiologist	LDN NICHD
OTHERS:	R. Pun	Visiting Fellow	LDN NICHD
	W. Habig	Research Chemist	DBP BB
	A. Schaffner	Guest Worker	LNP NINCDS
	P. Sonderegger	Guest Worker	LDN NICHD
	G. Westbrook	PRAT Fellow	LDN NICHD
	D. Breneman	Staff Fellow	LDN NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Developmental Neurobiology

SECTION
Section on Neurobiology

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 9.5	PROFESSIONAL: 5.0	OTHER: 4.5
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The sensitivity of neuronal development to blockade of electrical activity has an abrupt onset during the seventh day in culture. Cholinergic neurons, but not neurons synthesizing or taking up gamma-amino butyric acid (GABA) are affected. The developmental defects produced by blockade of electrical activity can be prevented by conditioned medium from active (but probably not inactive) cultures. Catechol and indole amine receptors appear to be regulated by amine containing fibers and non-innervated cells exhibit marked deficiency in such receptors. The ionic time and voltage dependences for the anomalous rectifier in dorsal root ganglion neurons has been described, using voltage clamp techniques.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00089-08 LDN
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PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Pineal-pituitary Interactions

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	D.C. Klein	Physiologist	LDN	NICHD
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COOPERATING UNITS (if any)
Kevin Catt, Reproductive Biology Branch, NICHD; L. Tamarkin, NICHD

LAB/BRANCH
Laboratory of Developmental Neurobiology

SECTION
Neuroendocrinology

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.2	OTHER: 0
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Many life processes are regulated by the pituitary gland. This project studies how the pineal gland, influences pituitary function. The primary control of the pituitary gland is via the release of brain hormones. One of these hormones, luteinizing hormone releasing factor, regulates the release of a pituitary hormone necessary for normal reproduction, luteinizing hormone. A pineal secretion, melatonin, prevents the brain hormone from stimulating the release of luteinizing hormone. Similar effects are found using new synthetic derivatives or melatonin. The function of the pineal gland is drastically altered by environmental light and by drugs; pineal functions also changes markedly during development. Thus, it seems possible that as a result of these changes, and subsequent pineal-pituitary interactions, there will be significant changes in pituitary gland function resulting in turn in alterations in general health. Such an interaction may explain why the pineal gland can stop reproduction in certain animals when they are deprived of light. A second interaction of the pineal gland and the pituitary is through the pituitary adrenal axis. Studies have been performed to determine whether or not such a relationship exists in the rhesus monkey.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 HD 00093-08 LDN

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Mechanism of Action of Nerve Growth Factor

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	G. Guroff	Chief, Section on Intermediary Metabolism
OTHER	S. Hashimoto	Visiting Fellow
	V. Zabrenetzky	Staff Fellow
	A. Togari	Visiting Fellow
	G. Dickens	Bio Lab Tech
	N. Tolson	Biologist

COOPERATING UNITS (if any)

P. Marangos, M, LCS; C. Londos, A, LNE

LAB/BRANCH

Laboratory of Developmental Neurobiology

SECTION

Section on Intermediary Metabolism

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, MD 20205

TOTAL MANYEARS:

6.0

PROFESSIONAL:

4.0

OTHER:

2.0

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS

(b) HUMAN TISSUES

(c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this work is to provide information on the mode of action of nerve growth factor. Nerve growth factor is required for the development and maintenance of the sympathetic and sensory nervous systems and may be a prototype of the many factors now known to be involved in the growth and maturation of various cell types. The mechanism of action is of interest because it should lead to an understanding of the way in which gene expression is regulated in neurons and how such factors induce the synthesis of specific enzymes for the biosynthesis of neurotransmitters or for the morphological changes necessary for the neuron to communicate with other cells through its ability to form synapses. In turn, such information may lead to an understanding of the development and differentiation of the non-dividing, non-replaceable neurons of the central nervous system and to information about the tumors which arise from them.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 HD 00094-12 LDN

PERIOD COVERED

October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Regulation of Neuroendocrine Metabolism: Circadian, Stress, Light and Drug Influences (rat, hamster, rhesus monkey)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	D.C. Klein	Physiologist	LDN	NICHD
OTHER	J.L. Weller	Chemist	LDN	NICHD

COOPERATING UNITS (if any)

R.Y. Moore, Dept. of Neurosciences, Univ. of CA, School of Medicine; R. Kvetnansky, LCS, NIMH; H. Hoffman, EBR, NICHD; M. Perlow and M. Mishkind, NIMH; S. Reppert, Harvard Medical School

LAB/BRANCH

Laboratory of Developmental Neurobiology

SECTION

Neuroendocrinology

INSTITUTE AND LOCATION

NIH, NICHD, Bethesda, MD 20205

TOTAL MANYEARS:

2.5

PROFESSIONAL:

2

OTHER:

0.5

CHECK APPROPRIATE BOX(ES)

- (a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER
- (a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to describe the factors which regulate the metabolism of a neuroendocrine organ, the pineal gland. These investigations are conducted within a hierarchy of levels of biological organization, including the interactions of the pineal gland with environmental lighting, stress, drugs, endocrine organs, and the central nervous system. Studies related to the central nervous system also probe the fundamental nature of the biological clock governing biological rhythms.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00095-12 LDN
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PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Regulation of Neuroendocrine Metabolism: Transsynaptic Mechanisms in the Pineal Gland

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. OTHER:	D.C. Klein J.L. Weller	Physiologist Biologist	LDN LDN	NICHD NICHD
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COOPERATING UNITS (if any)
D. Auerbach, Duke University

LAB/BRANCH
Laboratory of Developmental Neurobiology

SECTION
Neuroendocrinology

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.5	OTHER: 0.5
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINDRS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project focuses on the transsynaptic mechanisms which are important in regulating metabolism of a neuroendocrine tissue, the pineal gland. The specific topics of interest include the interaction during differentiation of the pineal gland and innervating structures, the role of nerves in both releasing and taking up transmitters, the interaction of transmitters in transsynaptic regulation and the characterization of postsynaptic adrenergic receptors.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00096-12 LDN
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PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Regulation of Neuroendocrine Metabolism: Intracellular Mechanisms

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	D.C. Klein	Physiologist	LDN	NICHD
OTHER:	A. Namboodiri	Visiting Associate	LDN	NICHD
	J.L. Weller	Biologist	LDN	NICHD
	D. Sugden	Visiting Fellow	LDN	NICHD

COOPERATING UNITS (if any)
K.L. Kirk, LC, NIAMMD: J. Pierce, OD, NHLI: G. Kapatos, S. Kaufmann D. Goldman, C. Merrill, NIMH

LAB/BRANCH
Laboratory of Developmental Neurobiology

SECTION
Neuroendocrinology

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.5	OTHER: 0.5
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Investigations have centered on understanding on a molecular level the intracellular regulation of metabolism in a neuroendocrine organ, the pineal gland. The topics of specific interest include the factors regulating cyclic AMP production, the function of cyclic AMP, the control of synthesis of pineal N-acetyltransferase activity, the control of activation and inactivation of this enzyme and related enzymes, the role of mRNA synthesis in the regulation of the activity of N-acetyltransferase activity, the regulation of pineal biopterin and control of guanosine cyclohydrolase.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRANURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00097-12 LDN
PERIOD COVERED October 1, 1981 through September 30, 1982		
TITLE OF PROJECT (80 characters or less) Regulation of Neuroendocrine Metabolism: Melatonin Physiology (rat, hamster, rhesus monkey)		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
P.I. OTHER:	D.C. Klein D. Sugden	Physiologist Visiting Fellow
		LDN LDN
		NICHD NICHD
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Developmental Neurobiology		
SECTION Neuroendocrinology		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205		
TOTAL MANYEARS: 2.5	PROFESSIONAL: 2.0	OTHER: 0.5
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords)		
<p>Efforts are directed at fully describing the physiology of a putative neuroendocrine hormone, <u>melatonin</u>. Current interest is centered on describing the amount of <u>this compound</u> present in body fluids throughout life, and understanding the factors controlling circulating melatonin.</p>		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00700-05 LDN																				
PERIOD COVERED October 1, 1981 to September 30, 1982																						
TITLE OF PROJECT (80 characters or less) Cell interactions in synaptogenesis																						
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0"> <tr> <td>PI:</td> <td>P. Sonderegger</td> <td>Guest Worker</td> <td>LDN NICHD</td> </tr> <tr> <td></td> <td>C.N. Christian</td> <td>Staff Fellow</td> <td>LDN NICHD</td> </tr> <tr> <td></td> <td>P.G. Nelson</td> <td>Chief, Lab. Dev. Neurobiol.</td> <td>LDN NICHD</td> </tr> <tr> <td>OTHERS:</td> <td>P. Pudimat</td> <td>Bio. Lab. Tech.</td> <td>LDN NICHD</td> </tr> <tr> <td></td> <td>A. Schaffner</td> <td>Guest Worker</td> <td>LNP NINCDS</td> </tr> </table>			PI:	P. Sonderegger	Guest Worker	LDN NICHD		C.N. Christian	Staff Fellow	LDN NICHD		P.G. Nelson	Chief, Lab. Dev. Neurobiol.	LDN NICHD	OTHERS:	P. Pudimat	Bio. Lab. Tech.	LDN NICHD		A. Schaffner	Guest Worker	LNP NINCDS
PI:	P. Sonderegger	Guest Worker	LDN NICHD																			
	C.N. Christian	Staff Fellow	LDN NICHD																			
	P.G. Nelson	Chief, Lab. Dev. Neurobiol.	LDN NICHD																			
OTHERS:	P. Pudimat	Bio. Lab. Tech.	LDN NICHD																			
	A. Schaffner	Guest Worker	LNP NINCDS																			
COOPERATING UNITS (if any) Laboratory of Biochemical Genetics, NHLBI; Laboratory of Biophysics, NINCDS;																						
LAB/BRANCH Laboratory of Developmental Neurobiology																						
SECTION Section on Neurobiology																						
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205																						
TOTAL MANYEARS: 3.5	PROFESSIONAL: 1.5	OTHER: 2.0																				
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																						
SUMMARY OF WORK (200 words or less - underline keywords) <p>The action of a <u>receptor aggregation factor</u> (RAF) produced specifically by <u>neurons</u> aggregates the <u>acetylcholine receptors</u> (AChR) on muscle. The action of the RAF is strongly <u>inhibited</u> by short exposure of the test system (myotubes plus RAF) to light. <u>Innervation</u> of <u>muscle</u> by <u>ciliary ganglion neurons</u> is decreased in a time dependent manner by <u>co-culture</u> with <u>spinal cord neurons</u> but not by <u>dorsal root ganglion neurons</u>.</p>																						

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00702-02 LDN
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) Genetics of Primate Vocal Behavior		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: J.D. Newman Research Physiologist LDN NICHD		
COOPERATING UNITS (if any) N.F. Ma, New England Regional Primate Research Center		
LAB/BRANCH Laboratory of Developmental Neurobiology		
SECTION Section on Brain and Behavior		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .75	PROFESSIONAL: .25	OTHER: 0.5
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) This project involves the study of the <u>inheritance</u> patterns of well-defined vocalizations, particularly the isolation call, in selected <u>primates</u> . Cross-breeding of closely related species or subspecies with distinct vocal differences provides the opportunity for analysis of the <u>parental contributions</u> to <u>hybrid vocal traits</u> . Collaboration with experts in cellular genetics provides information regarding the <u>transmission of genetic material</u> to hybrid offspring as well as the <u>genetic distances</u> between members of the parental populations. A variety of primate species are examined for distinctive vocal traits and production of viable interspecific hybrids to evaluate their usefulness for studies in this area of genetic research.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00703-02 LDN
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) Effect of long chain fatty acids on developing neurons in cell culture		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: D. E. Brenneman Staff Fellow LDN NICHD		
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Developmental Neurobiology		
SECTION Neurobiology		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 0.0	PROFESSIONAL: 0.0	OTHER: 0.0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) This project was inactive during FY82.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER <p style="text-align: center;">Z01 HD 00704-02 LDN</p>	
PERIOD COVERED October 1, 1981 to September 30, 1982			
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;">Physiologic Effects of Tetanus Toxin on Nerve Cells</p>			
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT			
PI:	G.K. Bergey H. Bigalke	Medical Officer Visiting Scientist	LDN, NICHD LDN, NICHD
Others:	P.G. Nelson S. Fitzgerald	Chief, Lab. of Dev. Neurobiol. Biologist	LDN, NICHD LDN, NICHD
COOPERATING UNITS (if any) <p style="text-align: center;">W. Habig, Bureau of Biologics, FDA</p>			
LAB/BRANCH Laboratory of Developmental Neurobiology			
SECTION Section on Neurobiology			
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205			
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:	
1.0	1.0	0	
CHECK APPROPRIATE BOX(ES)			
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER			
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS			
SUMMARY OF WORK (200 words or less - underline keywords)			
<p> <u>Tetanus toxin</u> produces a gradual <u>decrease</u> in <u>transmitter output</u> from both <u>excitatory</u> and <u>inhibitory synapses</u>. <u>Inhibitory synapses</u> are <u>preferentially affected</u> and this relative decrease of <u>inhibitory synaptic action</u> accounts for the <u>convulsant action</u> of the toxin. </p>			

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00705-01 LDN												
PERIOD COVERED October 1, 1981 to September 30, 1982														
TITLE OF PROJECT (80 characters or less) Macromolecules involved in the intracellular and intercellular organization of neurons														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width:100%; border: none;"> <tr> <td style="width:15%;">PI:</td> <td style="width:60%;">H. Gainer Chief, Sec. on Functional Neurochemistry</td> <td style="width:25%;">LDN NICHD</td> </tr> <tr> <td>Others:</td> <td>J.T. Russell Staff Fellow</td> <td>LDN NICHD</td> </tr> <tr> <td></td> <td>Y. Ben-Barak Guest Worker</td> <td>LDN NICHD</td> </tr> <tr> <td></td> <td>M. Whitnall Guest Worker</td> <td>LDN NICHD</td> </tr> </table>			PI:	H. Gainer Chief, Sec. on Functional Neurochemistry	LDN NICHD	Others:	J.T. Russell Staff Fellow	LDN NICHD		Y. Ben-Barak Guest Worker	LDN NICHD		M. Whitnall Guest Worker	LDN NICHD
PI:	H. Gainer Chief, Sec. on Functional Neurochemistry	LDN NICHD												
Others:	J.T. Russell Staff Fellow	LDN NICHD												
	Y. Ben-Barak Guest Worker	LDN NICHD												
	M. Whitnall Guest Worker	LDN NICHD												
COOPERATING UNITS (if any) H.C. Pant, Alcohol and Drug Abuse, NIMH I. Tasaki, Laboratory of Neurophysiology, NIMH K. Ozato, NICHD; R. Pruss, Lab. of Clinical Science, NIMH														
LAB/BRANCH Laboratory of Developmental Neurobiology														
SECTION Section on Functional Neurochemistry														
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland														
TOTAL MANYEARS: 0.7	PROFESSIONAL: 0.7	OTHER: 0												
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINDRS <input type="checkbox"/> (a2) INTERVIEWS														
SUMMARY OF WORK (200 words or less - underline keywords) <p>A <u>calcium-activated protease</u> which specifically degrades <u>neurofilaments</u> has been studied. The characteristics of this protease indicate that it may be involved in formation of nerve terminals during development. <u>Covalent labeling techniques</u> developed in our laboratory suggest that there is a <u>slow retrograde transport</u> wave in mammalian nerves which contains <u>serum albumin</u>. Analysis of <u>neurosecretory vesicle membrane proteins</u> have led to the finding of two monoclonal antibodies which react specifically with two membrane proteins. Using <u>monoclonal antibodies</u> against <u>H-2</u> and <u>Thy-1</u> antigens in immunocytochemical experiments on mouse brain shows that selective brain cells contain these antigenic determinants.</p>														

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Laboratory of Molecular Genetics

Project Number	Title	Principal Investigator
Z01 HD 00066 -12	Control of Mechanisms in Temperate Bacteriophage λ	Robert Weisberg
Z01 HD 00067 -14	Integrative Control of Macromolecular Synthesis	Michael Cashel
Z01 HD 00068 -11	Factors Influencing Genetic Transcription-Initiation and Termination	Robert J. Crouch
Z01 HD 00069 -10	Molecular Aspects of the Replication of Enveloped Animal RNA Viruses	Judith G. Levin
Z01 HD 00070 -22	Morphogenesis of Animal Viruses During Infection of Mammalian Cells	Jacob V. Maizel, Jr.
Z01 HD 00071 -10	Study of Adenovirus Gene Functions	Heiner Westphal
Z01 HD 00073 -11	Regulation of Immune Systems at the Cellular Level	Edgar E. Hanna
Z01 HD 00074 -11	Regulated Gene Expression During Cell Growth and Differentiation	Philip Leder
Z01 HD 01000 -03	The Molecular Genetics of the Major Histocompatibility Complex	Jonathan G. Seidman

Laboratory of Molecular Genetics

The Laboratory of Molecular Genetics conducts research directed towards understanding the molecular processes involved in the transmission of genetic information and its regulated expression during growth and differentiation. A variety of model systems are under investigation, ranging from bacterial and animal viruses to complex vertebrate regulatory responses involving the synthesis of specific antibodies and the development of specific organ systems. Taken together, the Laboratory joins active workers in the areas of genetics, biochemistry, electron microscopy, immunology, virology and cellular biology to bring their skills to bear on problems of mutual interest. The year covered by this Report has seen important changes in the Laboratory of Molecular Genetics. The group headed by Dr. Joram Piatigorsky left the Laboratory at the beginning of the year, and the groups headed by Dr. Philip Leder and Dr. Jonathan Seidman left during the year. In the latter part of the reporting period the Laboratory consisted of seven research groups distributed among five sections. The arrival of additional research groups is expected shortly and should re-establish research activity in the Laboratory to the appropriate level.

I. Section on Gene Organization and Control

A. The aim of this project is to understand the regulated expression of the globin and immunoglobulin genes of man and the mouse. In order to do this the human and murine kappa and lambda light chain and heavy chain genes have been cloned; the alpha and beta globin genes and pseudogenes of the mouse were also cloned. Detailed structural studies have been carried out that allow certain critical inferences about mechanisms and nucleotide sequences that are involved in the transcriptional activation, somatic rearrangement and evolution of some of these genetic sequences. In particular, a new class of genetic elements that appears to have arisen via RNA intermediates have been defined. Experiments have established features of the human lambda and IgE loci and chromosomally mapped a number of the human Ig genes to bands involved in characteristic translocations. The structural requirements for globin gene promoter activity have also been detailed. (Dr. Philip Leder -- Principal Investigator)

B. Studies have been directed towards understanding the regulatory and control pathways in immune systems at the cellular level. The coordinated roles of regulatory and effector lymphocytes, and macrophages are being delineated in a T-cell dependent model immune system in vitro. This model involves our capacity to fully complement the T-cell dependent antibody responses of NFR/N nude (nu/nu) mouse splenocytes (B-cells and macrophages) to haptenic immunogens in vitro by the addition of T-cells fractionated from phenotypically normal +/nu splenocytes. Monoclonal and perpetual cell lines (hybridomas) are constructed by fusion of naturally occurring malignant cells with cells fractionated from populations expressing an activity of interest. The resulting hybrid cells are cloned, classified by cell surface markers, tested for function and stored in liquid nitrogen. A library of functional cell clones is being constructed which consist of members that express most of the various activities ascribed to cells of the immune system. This includes helper, suppressor, and cytotoxic clones. Microbial and plant agents are known to variously affect the immune system in animals and humans. This natural circumstance is being exploited in our attempt to understand pathways toward the regulation of the immune system. A streptococcal protein (SPE, an exotoxin) was shown to profoundly cancel the activity of normal suppressor T-lymphocytes in experimental antibody responses to haptenic immunogens. In recent experiments we have been able to distinguish and separate two populations of T-lymphocytes. One responds to SPE while the other does not. This has allowed us to formulate two alternative models of the development of immune regulation by T-cells. One is that suppression and help are different functions associated with the same T-cells but at different stages of their development. The other is that suppression and help are different functions of different T-cell lineages. In the former, SPE could drive the development selectively along the helper course. In the latter, SPE could inactivate the suppressor population causing an unbalanced helper activity. Precursors of T-cell clones have also been constructed. It now appears clear that while SPE cancels the activity of suppressor clones, it is also capable of driving precursor clones to initiate development. Thus this approach should facilitate our attempts to understand and to map the various regulatory phenotypes within immune systems. (Dr. Edgar E. Hanna -- Principal Investigator).

C. The goal of this project is to define the molecular mechanisms involved in the replication of enveloped RNA viruses and in particular, to understand the factors which influence the regulation and expression of viral genetic information. Studies are being carried out with the murine leukemia virus system. Current interest is focused on the process of reverse transcription in an effort to correlate genetic structure with enzymatic function. A nonconditional viral mutant which is defective in the pol gene has been shown to produce an abnormally small enzyme with reduced polymerase activity, although its genome size is the same as wild type. Recombinant DNA technology is being used to map the genetic lesion in this mutant. In addition, the defect in enzymatic synthesis of viral DNA is being analyzed in more detail. Another interest concerns the potential use of frog oocytes to study transcription and processing of viral genes. Experiments are in progress to determine whether viral RNA and proteins are expressed following injection of molecularly cloned viral DNA. (Dr. Judith G. Levin -- Principal Investigator)

D. The aim of this project is to define the genetic basis of cell-cell recognition. As a first step, the genes encoding the major histocompatibility antigens (transplantation antigens) and the Ia antigens (immune associated antigens) are being characterized by the use of recombinant DNA technology. The initial efforts have been directed towards obtaining cloned DNAs corresponding to these genes. During the past year a cDNA clone for the murine I-A β chain has been isolated. The structure, evolution, and expression of the single murine β 2-microglobulin gene and the multiple H-2-like genes are being studied with the aid of the cloned cDNAs. (Dr. Jonathan G. Seidman--Principal Investigator)

II. Section on Molecular Structure

A. Studies have been directed towards understanding the structure of the human virus, poliovirus, rhinovirus, and adenovirus, and the way they gain control of most cell molecular processes. Work has continued on the cloning of rhinovirus type 14 and poliovirus type I cDNA. Isolated strands of adenovirus DNA fragments have been incorporated into liposomes and introduced into cells in order to study their expression either in production of new products or through perturbation of intracellular processes. New programs have been developed to analyze nucleic acid and protein sequences. Important improvements in programs to predict secondary structures and to automatically draw predicted structures have been employed in analyzing viral and cellular sequences. Growing concordance between predicted structures and observed properties is being achieved. (Dr. Jacob V. Maizel, Jr.--Principal Investigator)

III. Section on Animal Viruses

A. Eukaryotic gene control is the general topic of three studies presently performed in this laboratory. The first of these deals with early adenovirus gene regulation. We have detected a regulatory cascade and are presently working out the molecular details of viral gene communications. The second study concerns host cell dependent rearrangements in the genome of adeno-SV40-hybrid virus. In collaboration with Dr. A. Lewis, Jr., the possibility is investigated that the observed genomic changes are directed by constraints in RNA processing. The third study was started in early 1982 and involves gene transfer into early stage mouse embryos. The goal of this line of experiments is to study the expression and control of a defined set of genes in the developing mouse embryo. We have familiarized ourselves with the techniques of DNA injection into mouse zygotes and reimplantation of zygotes into foster mothers and are presently injecting a signal gene (E. coli chloramphenicol transacetylase) which was placed under the control of a variety of eukaryotic promoters. Integration and expression of this gene is monitored after birth of live offspring. (Dr. Heiner Westphal -- Principal Investigator)

IV. Section on Molecular Regulation

A. The goal of this project is understanding how a cell coordinates the expression of its genetic repertoire as a function of growth rate and nutritional sufficiency. Previous annual reports have concerned genetic and physiological characterization of guanosine 3', 5'-bispyrophosphate (ppGpp) which has emerged as a major signal regulating these processes and the three regulatory mechanisms affecting the intracellular concentration of ppGpp. Regulation of ribosomal RNA cistron expression has long been the paradigm of coordinate gene-expression but the mechanism by which this occurs has been elusive. This year we report finding a means of measuring the in vivo regulatory effects of ppGpp on rRNA cistron expression directly on RNA transcripts using plasmids bearing fusions of ribosomal tandem promoter and terminator regions. The upstream promoter is sensitive to ppGpp whereas the downstream promoter is unexpectedly insensitive to ppGpp but nevertheless sensitive to growth rate by an unknown mechanism. Transcription elongation and termination are unaffected by ppGpp. The metabolic stability of transcripts is unexpectedly prolonged by inhibition of protein synthesis independent of ppGpp. We have preliminary indications of ribosomal RNA promoter specific antiterminator activity allowing read through of normally efficient terminators. (Dr. C. Michael Cashel -- Principal Investigator)

B. The goal of this project has been to understand the control of synthesis and utilization of RNA transcripts at the enzymological level.

A major advance was made in the attempt to understand the role and mechanism of ribonuclease H. This advance is based on the determination of the nucleotide sequence coding for E. coli RNase H and for a mutant reported earlier (Carl, P. L., Bloom, L. and Crouch, R. J. J. Bacteriology 144:28-35, 1980). The gene sequence predicts a protein of 155 amino acids (17,600 daltons). Confirmation of the sequence was established by purifying RNase H to near homogeneity by a new procedure and determining both the amino acid composition and the amino terminal sequence of the purified protein.

The ribonuclease H level in the mutant cell is 0.1 that of the wild type cell. In cells bearing plasmids into which the RNase H gene is cloned, the level of RNase H increases to 15 times the wild type amount. Thus, the range in RNase H concentration that the cell can tolerate is at least 150 fold (0.1 to 15x the normal amount).

The gene sequence for the mutant shows a single base change such that the protein is altered 12 amino acids from the carboxy terminus. A change from proline to leucine accounts for the lower specific activity in the mutant protein. (Dr. Robert J. Crouch -- Principal Investigator)

V. Section on Microbial Genetics

A. The long term goal of the project is to determine the mechanism of recombination of virus DNA with the host chromosome (site-specific recombination). Recombination between the bacteriophage lambda and its host *Escherichia coli* involves specialized regions in each DNA called attachment (att) sites. This phage and bacterial att sites share only 15 nucleotide pairs of homology, within which crossing over occurs. Three mutations that change the specificity of site-specific recombination have been isolated and sequenced. The mutations are located in a 7 base pair segment of the att site called the overlap region, located within the 15 base pair homologous segment. All three of these mutations depress recombination when they are present in only one att site of a pair, but recombination is restored when the same mutation is present in both sites. This strongly argues that recombination between att sites is promoted by a direct interaction between identical nucleotides of the two participating overlap regions. A specialized transducing phage has been isolated that carries a host gene whose product is required for site-specific recombination. Use of this phage has allowed construction of a restriction map of the gene, and this information will be used to help determine its DNA sequence. The characterization of endonuclease VII has been continued -- an enzyme that has been shown cleaves an intermediate in genetic recombination known as a Holliday structure. The products of enzyme action are two unbranched double-stranded DNA molecules, each with a single nick. The nicks can be sealed with DNA ligase. Thus, endonuclease VII and DNA ligase can resolve a recombination intermediate into intact, genetically sensible products. (Dr. Robert A. Weisberg - Principal Investigator)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00066-12 LMG
PERIOD COVERED October 1, 1981 through September 30, 1982		
TITLE OF PROJECT (80 characters or less) Control Mechanisms in Temperate Bacteriophage λ		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Robert A. Weisberg OTHERS: Eric Flamm Staff Fellow LMG NICHD Edward Appelbaum Staff Fellow LMG NICHD		
COOPERATING UNITS (if any) Dr. A. Landy, Brown University, Providence, R. I. Dr. Howard Nash, LNC, NIMH Dr. K. Mizuuchi, LMB, NIAMDD		
LAB/BRANCH Laboratory of Molecular Genetics		
SECTION Section on Microbial Genetics		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 2.75	PROFESSIONAL: 2.75	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The long term goal of this project is to determine the mechanism of recombination of virus DNA with the host chromosome (<u>site-specific recombination</u>). Recombination between the <u>bacteriophage λ</u> and its host <u>Escherichia coli</u> involves specialized regions in each DNA called attachment (<u>att</u>) sites. We have isolated and sequenced three mutations that change the specificity of site-specific recombination. The mutations are located in a 7 base pair segment of the <u>att</u> site called the overlap region. The properties of these mutations strengthen our conclusion that recombination between <u>att</u> sites requires a direct interaction between identical nucleotides of the two participating overlap regions. We have isolated a specialized transducing phage that carries a host gene whose product is required for site-specific recombination. Use of this phage has enabled us to construct a restriction map of the gene. We found that a mutation that increases the efficiency of site-specific recombination is located within the phage <u>int</u> gene. We have continued our characterization of endonuclease VII -- an enzyme that cleaves an intermediate in genetic recombination known as a <u>Holliday structure</u> . The products of enzyme action are two unbranched double-stranded DNA molecules each with a single nick. The nicks can be sealed with DNA ligase.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00067-14 LMG
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PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Integrative Control of Macromolecular Synthesis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Michael Cashel	Medical Research Officer	LMG NICHD
OTHERS:	Sara Contente	Staff Fellow	LMG NICHD
	Paolo Sarmientos	Visiting Fellow	LMG NICHD
	Gianni Chinali	Visiting Scientist	LMG NICHD

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Molecular Genetics

SECTION
Section on Molecular Regulation

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 3.2	PROFESSIONAL: 3.2	OTHER:
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The goal of this project is understanding how a cell coordinates the expression of its genetic repertoire as a function of growth rate and nutritional sufficiency. Previous annual reports have concerned genetic and physiological characterization of guanosine 3',5'-bispyrophosphate (ppGpp) which has emerged as a major signal regulating these processes and the three regulatory mechanisms affecting the intracellular concentration of ppGpp. Regulation of ribosomal RNA cistron expression has long been the paradigm of coordinate gene-expression but the mechanism by which this occurs has been elusive. This year we report finding a means of measuring the in vivo regulatory effects of ppGpp on rRNA cistron expression directly on RNA transcripts using plasmids bearing fusions of ribosomal tandem promoter and terminator regions. The upstream promoter is sensitive to ppGpp whereas the downstream promoter is unexpectedly insensitive to ppGpp but nevertheless sensitive to growth rate by an unknown mechanism. Transcription elongation and termination are unaffected by ppGpp. The metabolic stability of transcripts is unexpectedly prolonged by inhibition of protein synthesis independent of ppGpp. We have preliminary indications of ribosomal RNA promoter specific antiterminator activity allowing read through of normally efficient terminators.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00068-11 LMG												
PERIOD COVERED October 1, 1981 through September 30, 1982														
TITLE OF PROJECT (80 characters or less) Factors Influencing Genetic Transcription-Initiation and Termination														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width:100%; border: none;"> <tr> <td style="width:15%;">PI:</td> <td style="width:35%;">Robert J. Crouch</td> <td style="width:25%;">Research Chemist</td> <td style="width:25%;">LMG NICHD</td> </tr> <tr> <td>OTHERS:</td> <td>Shigenori Kanaya</td> <td>Visiting Fellow</td> <td>LMG NICHD</td> </tr> <tr> <td></td> <td>Stephanie Seidman</td> <td>Staff Fellow</td> <td>LMG NICHD</td> </tr> </table>			PI:	Robert J. Crouch	Research Chemist	LMG NICHD	OTHERS:	Shigenori Kanaya	Visiting Fellow	LMG NICHD		Stephanie Seidman	Staff Fellow	LMG NICHD
PI:	Robert J. Crouch	Research Chemist	LMG NICHD											
OTHERS:	Shigenori Kanaya	Visiting Fellow	LMG NICHD											
	Stephanie Seidman	Staff Fellow	LMG NICHD											
COOPERATING UNITS (if any)														
LAB/BRANCH Laboratory of Molecular Genetics														
SECTION Section on Molecular Regulation														
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205														
TOTAL MANYEARS: 2.25	PROFESSIONAL: 2.25	OTHER: 0												
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS														
SUMMARY OF WORK (200 words or less - underline keywords) RNA plays an important role in cellular regulation--either by its presence in active form or by its total absence. A number of proteins have been shown to be involved in regulating RNA synthesis and RNA processing in <u>Escherichia coli</u> --among these are <u>RNA polymerase</u> , <u>rho</u> and <u>RNase III</u> . We have described an enzyme from chick embryos (RNase DII) which is an analogue of RNase III. These proteins are involved in the synthesis or inhibition of synthesis of specific species of RNA and in the <u>processing of RNA</u> . Another enzyme which may be involved in regulation of RNA synthesis is <u>RNase H</u> . To better understand the nature of this enzyme, we have determined the nucleotide sequences coding for <u>E. coli RNase H</u> and for a mutant of <u>E. coli RNase H</u> . Clones bearing plasmids of the wild-type RNase H gene produce 10-20 x the normal level of enzyme. Analogous clones of the mutant gene also produce 10-20 x the normal level of enzyme but with a lower specific activity. The objective of this research project is to determine the method by which several of these enzymes act to regulate RNA synthesis in <u>E. coli</u> and <u>chick embryos</u> .														

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00069-10 LMG
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PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Molecular Aspects of the Replication of Enveloped Animal RNA Viruses

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Judith G. Levin Research Biochemist LMG NICHD
OTHERS: Lesley I. Messer Postdoctoral Fellow LMG NICHD

COOPERATING UNITS (if any)
Brenda Gerwin, Laboratory of Molecular Oncology, NCI
Alan Rein, Biological Carcinogenesis Program, FCRF

LAB/BRANCH
Laboratory of Molecular Genetics

SECTION
Section on Gene Organization and Control

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.0	OTHER: 1.0
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The goal of this project is to define the molecular mechanisms involved in the replication of enveloped RNA viruses and in particular, to understand the factors which influence the regulation and expression of viral genetic information. Studies are being carried out with the murine leukemia virus system. Current interest is focused on the process of reverse transcription in an effort to correlate genetic structure with enzymatic function. A nonconditional viral mutant which is defective in the pol gene has been shown to produce an abnormally small enzyme with reduced polymerase activity, although its genome size is the same as wild type. Recombinant DNA technology is being used to map the genetic lesion in this mutant. In addition, the defect in enzymatic synthesis of viral DNA is being analyzed in more detail. Another interest concerns the potential use of frog oocytes to study transcription and processing of viral genes. Experiments are in progress to determine whether viral RNA and proteins are expressed following injection of molecularly cloned viral DNA.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00070-22 LMG																								
PERIOD COVERED October 1, 1981 through September 30, 1982																										
TITLE OF PROJECT (80 characters or less) Morphogenesis of Animal Viruses During Infection of Mammalian Cells																										
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0" style="width: 100%;"> <tr> <td style="width: 15%;">PI:</td> <td style="width: 40%;">Jacob V. Maizel, Jr.</td> <td style="width: 25%;">Research Chemist</td> <td style="width: 20%;">LMG NICHD</td> </tr> <tr> <td>OTHERS:</td> <td>Margaret Stewart</td> <td>Chemist</td> <td>LMG NICHD</td> </tr> <tr> <td></td> <td>Robert P. Lenk</td> <td>Staff Fellow</td> <td>LMG NICHD</td> </tr> <tr> <td></td> <td>Charles McLean</td> <td>Staff Fellow</td> <td>LMG NICHD</td> </tr> <tr> <td></td> <td>Kathleen Currey</td> <td>Research Associate</td> <td>LMG NICHD</td> </tr> <tr> <td></td> <td>John Owens</td> <td>Chemist</td> <td>LMG NICHD</td> </tr> </table>			PI:	Jacob V. Maizel, Jr.	Research Chemist	LMG NICHD	OTHERS:	Margaret Stewart	Chemist	LMG NICHD		Robert P. Lenk	Staff Fellow	LMG NICHD		Charles McLean	Staff Fellow	LMG NICHD		Kathleen Currey	Research Associate	LMG NICHD		John Owens	Chemist	LMG NICHD
PI:	Jacob V. Maizel, Jr.	Research Chemist	LMG NICHD																							
OTHERS:	Margaret Stewart	Chemist	LMG NICHD																							
	Robert P. Lenk	Staff Fellow	LMG NICHD																							
	Charles McLean	Staff Fellow	LMG NICHD																							
	Kathleen Currey	Research Associate	LMG NICHD																							
	John Owens	Chemist	LMG NICHD																							
COOPERATING UNITS (if any) Dr. L. Lipkin, DCBC, NCI; Dr. B. Shapiro, DCBC, NCI; Dr. G. vande Woude, VB, NCI; Dr. J. Piatigorsky, LMB, NEI; Dr. R. Dhar, LMV, NCI.																										
LAB/BRANCH Laboratory of Molecular Genetics																										
SECTION Section on Molecular Structure																										
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205																										
TOTAL MANYEARS: 5.50	PROFESSIONAL: 5.50	OTHER: 0																								
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																										
SUMMARY OF WORK (200 words or less - underline keywords) Mammalian virus systems have been studied by combined electron microscopic and biochemical methods. Polio and rhinovirus RNA fragments have been translated <u>in vitro</u> , and <u>cloned</u> in plasmids. Adenovirus early proteins have been localized <u>in the cellular ultrastructure</u> . Late viral protein expression has been perturbed by introduction of anti-cellular antibodies in liposomes. Newly devised computer programs have been used to analyze nucleics for <u>homologies</u> , <u>secondary structures</u> , <u>splice sites</u> , <u>promoter sites</u> and <u>recombination sites</u> .																										

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00071-10 LMG
PERIOD COVERED October 1, 1981 through September 30, 1982		
TITLE OF PROJECT (80 characters or less) Study of Adenovirus Gene Functions (a) Adenovirus Gene Controls (b) Gene Transfer Into Mice		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI: OTHERS:	H. Westphal W. Richardson S.-P. Lai S. Fisher P. Overbeek J. Khillan	Research Geneticist Visiting Fellow Chemist Staff Fellow Staff Fellow Visiting Fellow
		LMG NICHD LMG NICHD LMG NICHD LMG NICHD LMG NICHD LMG NICHD
COOPERATING UNITS (if any) Andrew Lewis, LVD, NIAID		
LAB/BRANCH Laboratory of Molecular Genetics		
SECTION Section on Animal Viruses		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 4.7	PROFESSIONAL: 3.7	OTHER: 1.0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) <u>Eukaryotic gene control</u> is the general topic of three studies presently performed in my laboratory. The first of these deals with early <u>adenovirus</u> gene regulation. We have detected a regulatory cascade and are presently working out the molecular details of viral gene communications. The second study concerns host cell dependent rearrangements in the genome of <u>adeno-SV40-hybrid virus</u> . In collaboration with Dr. A. Lewis, Jr., we investigate the possibility that the observed genomic changes are directed by constraints in RNA processing. The third study was started in early 1982 and involves gene transfer into early stage mouse embryos. The goal of this line of experiments is to study the expression and control of a defined set of genes in the developing <u>mouse embryo</u> . We have familiarized ourselves with the techniques of DNA injection into mouse zygotes and reimplantation of zygotes into foster mothers and are presently injecting a signal gene (E. coli chloramphenicol transacetylase) which was placed under the control of a variety of eukaryotic promoters. Integration and expression of this gene is monitored after birth of live offspring.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00073-11 LMG
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PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)
Regulation of Immune Systems at the Cellular Level

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Edgar E. Hanna	Research Microbiologist	LMG NICHD
OTHER:	Glenda C. Webb	Staff Fellow	LMG NICHD
	Prince K. Arora	Staff Fellow	LMG NICHD

COOPERATING UNITS (if any)
C. T. Hansen, Geneticist, VR, DRS, NIH

LAB/BRANCH
Laboratory of Molecular Genetics

SECTION
Section on Gene Organization and Control

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2.85	PROFESSIONAL: 2.75	OTHER: 0.1
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Experiments are directed toward understanding processes by which the immune system is regulated at the cellular level. The integrated pathways of the cascade of regulatory cells such as macrophages, thymus-derived helper and suppressor T-cells, as well as the B-cells are being mapped. We are seeking to understand cell circuitry from the precursor stage through the various phenotypic stages between suppressor and helper functional stages. Our results involving the preferential activation/or inactivation of the suppressor function of T-cells by natural microbial agents such as the streptococcal exotoxin, SPE, have delineated a novel approach towards understanding regulatory pathways and T-cell circuitry in the immune system. We have recently achieved stabilization of several helper T-cell phenotypes as functional T-cell hybridomas. We have progressed also towards establishing cell clones which may express an effector cell (cytotoxic or killer) phenotype. This approach is facilitating the ascertainment of definitive regulatory roles of T-cells. These monoclonal and perpetual T-cell clones also provide stable cellular targets for understanding the mechanisms of interference by microbes, their inhibitors, and their mitogens in immune systems.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00074-11 LMG	
PERIOD COVERED October 1, 1981 through May 30, 1982			
TITLE OF PROJECT (80 characters or less) Regulated Gene Expression During Cell Growth and Differentiation			
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT			
PI: OTHERS:	P. Leder J. Battey P. Hieter G. Hollis K. Kelly I. Kirsch J. Ravetch U. Siebenlist C. Talkington	Guest Worker Guest Worker Postdoctoral Fellow Staff Fellow Staff Fellow Research Associate Research Associate Visiting Fellow Staff Fellow	LMG NICHD LMG NICHD LMG NICHD LMG NICHD LMG NICHD LMG NICHD LMG NICHD LMG NICHD
COOPERATING UNITS (if any) S. Korsmeyer and T. Waldmann, MB, NCI; J. Seidman, LMG, NICHD; D. Swan and O.W. McBride, CIP, NCI.			
LAB/BRANCH Laboratory of Molecular Genetics			
SECTION Section on Gene Organization and Control			
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205			
TOTAL MANYEARS: 5.6	PROFESSIONAL: 4.1	OTHER: 1.5	
CHECK APPROPRIATE BOX(ES)			
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER			
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS			
SUMMARY OF WORK (200 words or less - underline keywords)			
<p> We wish to understand the regulated expression of the <u>globin</u> and <u>immunoglobulin genes</u> of <u>man</u> and the <u>mouse</u>. In order to do this we have <u>cloned</u> the human and murine kappa and lambda light chain and heavy chain genes; the alpha and beta globin <u>genes</u> and <u>pseudogenes</u> of the mouse were also cloned. Detailed structural studies have been carried out that allow us to make certain critical inferences about mechanisms and nucleotide sequences that are involved in the transcriptional activation, somatic rearrangement and evolution of some of these genetic sequences. In particular, we have defined a new class of genetic elements that appears to have arisen via RNA intermediates. We have established features of the human lambda and IgE loci and chromosomally mapped a number of the human Ig genes to bands involved in characteristic translocations. We have also detailed the structural requirements for globin gene promoter activity. </p>			

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD01000-03 LMG																								
PERIOD COVERED October 1, 1981 through May 30, 1982																										
TITLE OF PROJECT (80 characters or less) The Molecular Genetics of the Major Histocompatibility Complex																										
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0"> <tr> <td>PI:</td> <td>J.G. Seidman</td> <td>Senior Staff Fellow</td> <td>LMG NICHD</td> </tr> <tr> <td>OTHERS:</td> <td>G.A. Evans</td> <td>Research Associate</td> <td>LMG NICHD</td> </tr> <tr> <td></td> <td>D.H. Margulies</td> <td>Research Associate</td> <td>LMG NICHD</td> </tr> <tr> <td></td> <td>J.R. Parnes</td> <td>Guest Worker</td> <td>LMG NICHD</td> </tr> <tr> <td></td> <td>R.N. Germain</td> <td>Guest Worker</td> <td>LMG NICHD</td> </tr> <tr> <td></td> <td>R.R. Robinson</td> <td>Staff Fellow</td> <td>LMG NICHD</td> </tr> </table>			PI:	J.G. Seidman	Senior Staff Fellow	LMG NICHD	OTHERS:	G.A. Evans	Research Associate	LMG NICHD		D.H. Margulies	Research Associate	LMG NICHD		J.R. Parnes	Guest Worker	LMG NICHD		R.N. Germain	Guest Worker	LMG NICHD		R.R. Robinson	Staff Fellow	LMG NICHD
PI:	J.G. Seidman	Senior Staff Fellow	LMG NICHD																							
OTHERS:	G.A. Evans	Research Associate	LMG NICHD																							
	D.H. Margulies	Research Associate	LMG NICHD																							
	J.R. Parnes	Guest Worker	LMG NICHD																							
	R.N. Germain	Guest Worker	LMG NICHD																							
	R.R. Robinson	Staff Fellow	LMG NICHD																							
COOPERATING UNITS (if any) Dr. Ettore Appella, NCI																										
LAB/BRANCH Laboratory of Molecular Genetics																										
SECTION Section on Gene Organization and Control																										
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205																										
TOTAL MANYEARS: 5.0	PROFESSIONAL: 5.0	OTHER: 0																								
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																										
SUMMARY OF WORK (200 words or less - underline keywords) We are attempting to define the genetic basis of cell-cell recognition. As a first step, we plan to characterize the genes encoding the <u>major histocompatibility antigens</u> (transplantation antigens) and the <u>Ia antigens</u> (immune associated antigens) by the use of <u>recombinant DNA technology</u> . Our initial efforts have been directed towards obtaining cloned DNAs corresponding to these genes. During the past year we obtained a cDNA clone for the murine I-A β chain. The structure, evolution, and expression of the single murine β 2-microglobulin gene and the multiple H-2-like genes are being studied with the aid of the cloned cDNAs.																										

NICHD ANNUAL REPORT

October 1, 1981 through September 30, 1982

Child and Family Research Branch

Summary

<u>Project Number</u>	<u>Title</u>
Z01 HD 00012-06 CFR	The Development of Mastery Motivation in Infants
Z01 HD 00013-06 CFR	Role of Mother-Infant Relationship in Subsequent Socio-Emotional Development
Z01 HD 00014-06 CFR	Psychological Aspects of Childbearing and the Neonatal Period
Z01 HD 00015-05 CFR	Parent-Infant Interaction Subsequent to Cesarean Delivery
Z01 HD 00016-05 CFR	The Integration of Child Care and Work Roles
Z01 HD 00019-04 CFR	Mastery Motivation and Social Competence in Down Syndrome Infants
Z01 HD 01100-03 CFR	A Follow-up Study of Mastery Motivation
Z01 HD 01101-01 CFR	Naturally-Occurring Separations between Mother and Infant During the First Year of Life
Z01 HD 01102-01 CFR	Behavioral Correlates of Endocrine Disorders in Children
Z01 HD 01103-01 CFR	Sleep Ontogeny in Children with Precocious Puberty

Summary of Research Activities

The influence of early experiences in the family on the development of the young child continues to be an active focus of the research in the Branch. In progress are several studies of different aspects of family influence. One deals with the impact on the family of the mother's return to work during the first year of the child's life; another study is concerned with the adaptation of families in which a cesarean birth occurs. An ongoing study of attachment is examining some basic methodological issues regarding the assessment of attachment, in addition to considering the effects of cesarean section and the mother's employment on the developing mother-infant and father-infant relationship. Another study is exploring infants' reactions to brief, presumably non-traumatic, separations from the parents. Other investigations are concerned with the development of measures to assess the child's motivation for competence during the first year of life and its relationship to mastery motivation and competence in later childhood. The impact of stimulation by mother and father during the first year of life on mastery motivation is being studied as well. In all of these studies, the role of the father as well as the mother in the care of the infant and his relationship with the developing child are being investigated. In addition, analyses are in progress of data collected in a study of the significance of the husband-wife relationship during pregnancy and labor on the outcome of the pregnancy and the neonatal status of the child. This year, we have begun to explore behavioral-biological interrelationships through collaboration with the Developmental Endocrinology Branch in a study of the adaptation of children with precocious puberty and with Turner's syndrome.

In studying the psychological significance of cesarean childbirth, differences between cesarean and vaginal childbirth were found at 3 months of age in parent-infant interaction and in the parents' perceptions of their infants. Parents of cesarean-delivered infants provided less stimulation, they talked less to their infants and engaged in less caregiving behavior than did parents of vaginally delivered infants. Differences in parent-infant interaction at 3 months within the cesarean group, were related to whether or not the father was present at the birth of the child. The mother's mood during the early weeks with the infant was also related to the father's presence or absence during the delivery. Women whose husbands were not present during the birth process were more likely to be depressed.

With increasing numbers of mothers entering the work force, evaluation of its effects on the family and on parent infant interaction becomes important. In an ongoing study of maternal employment, differences were found at 3 months and at 12 months between families where the mother resumed employment and families in which she remained a full-time caregiver. Home observations of parent-infant interaction indicate that there are different caregiving patterns related to whether the mother (as well as the father) is employed. In dual wage-earner families, mothers tended to provide more stimulation than their husbands, while fathers in single wage-earner families exceeded their wives. This pattern was constant at the two age periods, although the specific behaviors affected were different.

For a long time, clinicians have emphasized the importance of early mother-infant attachment for later cognitive, social and emotional development. One problem has been how to assess the attachment relationship meaningfully. In a longitudinal study of early mother-infant attachment and its relation to later development, laboratory measures of attachment have been developed and data are being collected on families who were participants in the family and the mastery studies. The relation between early attachment to mother and father and later adaptation will be studied.

Increasingly, childbirth is recognized as a critical event in the early psychological development of the child and the adaptation of the family. It represents an interface of physiology and psychology which may be important for the emotional health of the infant and the parents. Several analyses have been completed during this year in a study of childbirth. One set of analyses found that the father's helpfulness during labor was positively related to his feelings of confidence in the fathering role; a puzzling finding was that closeness in the marital relationship prenatally was negatively related. The second set of analyses dealt with the effects of the electronic fetal monitoring equipment in the labor room. Among the findings were that much of father's and nurse's behavior while in the labor room involved attending to the fetal monitoring equipment or talking about it. Parents generally evaluated the fetal monitor positively, but did express some negative feelings. These data emphasize the importance of giving expectant parents information about the electronic fetal monitoring procedures and about the significance of the data provided by the monitor.

Although there have been a number of studies in recent years of competence and mastery motivation, little progress has been made in operationalizing the construct and developing measures to investigate the beginning of mastery behavior in infancy. Moreover, the roots of mastery motivation and the development of feelings of competence are not well understood. Our research on mastery motivation has been aimed at developing methods to study the beginnings of this behavior in infancy and exploring its roots. In the analyses which have been completed, significant relationships were found between the kinds of stimulation mothers and fathers give their infants and the infant's mastery motivation. At six months, sensory stimulation by fathers was related to the infant's persistence on problem-solving tasks. The impact of the mother's sensory stimulation was more generalized; it was related to overall mastery motivation. When the mother's and father's stimulation were combined, the relationship to persistence in problem solving was higher than for the behavior of either alone. Significant differences between fathers and mothers were found during home observations. Not surprisingly, fathers spent less time alone with their infants than mothers. However, of the time they are with infants, a much larger proportion of it consisted in playful interaction. In the time they were with the infants, they also engaged in significantly more teaching and sensory stimulation than mothers; these differences were stable from six to twelve months. There were no differences in father's or mother's responses to their infant's distress signals.

In a parallel study of mastery motivation and social competence in Down syndrome infants, data collection has been completed. Down syndrome infants compared with a matched sample of non-delayed infants showed lower levels of exploratory behavior and persistence in the Effect Production and Problem Solving components. There were no significant differences between the groups in the Practicing Sensori-motor Skills component, although the Down syndrome infants engaged in less exploratory

behavior and showed less persistence than did the control group. The findings of these studies in addition to contributing to our understanding of the origins of mastery add to our knowledge of the close interactions between motivational and cognitive development.

We have begun studies in the important area of behavioral-biological inter-relationships. Using a standardized questionnaire, the Child Behavior Checklist, collection of data has been initiated on the characteristics and adaptation of children with precocious puberty and with Turner's syndrome. The Checklist is given to the parents every six months. Preliminary analyses of the first 33 cases of the precocious puberty sample revealed that both boys and girls with precocious puberty manifest a significantly greater incidence of behavioral symptoms than the matched controls. For most of the scales, this difference can be attributed to a few cases scoring very highly, but on the depression scales, virtually all of the cases have high scores.

Publications Not Directly Related to a Specific Study.

Messer, D.J. Non-linguistic information which could assist the young child's interpretation of adult speech. In W. P. Robinson (Ed.), Interaction and Development. London: Academic Press, 1981.

Pedersen, F.A. Mother, father, and infant as an interactive system. In J. Belsky (Ed.), In the Beginning. New York: Columbia, 1982.

Rubenstein, J.L., Howes, C., and Pedersen, F.A. Second order effects of peers on mother-toddler interaction. Infant Behavior and Development, 1982, 5, 185-194.

Sostek, A.M., Vietze, P., Zaslów, M., Kreiss, L., Van der Waals, F., and Rubenstein, C. Social context in caregiver-infant interaction: Fais and the United States. In T. Field, A. Sostek, and H. Leiderman (Eds.), Culture and early interaction. Hillside, N.J.: LEA Press, 1981.

Yarrow, L.J. The many faces of continuity. Contemporary Psychology, 1981, 26, 746-747.

Yarrow, L.J. Perspectives on interactional research. In E. Shapiro and E. Weber (Eds.). Cognitive and affective growth: Developmental interaction. Hillsdale, N.J.: Lawrence Erlbaum Associates, 1981, pp. 97-108.

Zaslów, M., and Rogoff, B. The cross-cultural study of early interaction: Implications for research on culture and cognition. In T. Field, A. Sostek, and H. Leiderman (Eds.), Culture and early interaction. Hillside, N.J.: LEA Press, 1981.

Presentations Not Directly Related to a Specific Study.

Messer, D.J. The role that redundancy in adult-child communication could play in language acquisition. Invited paper presented at a conference on the Transition from Prelinguistic Communication: Issues and Implications. University of Delaware, September, 1981.

Messer, D.J., and Vietze, P.M. Organization in early mother-infant gaze. Paper given at the International Conference on Infant Studies, Austin, March, 1982.

Vietze, P.M., and Messer, D.J. The development of mother-infant vocal interaction in the first year of life. Paper given at the Southeastern Conference on Human Development, Baltimore, April, 1982.

Professional Activities

Staff members of the Child and Family Research Branch have been members of the boards of several organizations: the National Center for Clinical Infant Programs, the National Center for the Improvement of Childcare, the professional advisory council of the Parent and Child Association, the Alliance for Children, and the Professional Advisory Board for Understanding Children. One member of the staff is currently serving on the Credentials Committee of the Division of Developmental Psychology of the American Psychological Association. Another staff member is serving as Chairman of the Committee on Prevention, American Academy of Child Psychiatry.

Staff have been ad hoc reviewers for such journals as Child Development, Development Psychology, the Merrill-Palmer Quarterly Journal of Behavior and Development, Infant Behavior and Development, International Journal of Behavioral Development, Journal of Abnormal and Social Psychology, Journal of Nervous and Mental Diseases, Journal of Personality and Social Psychology, Journal of Child Psychology and Psychiatry, and Science. Members of the staff have also reviewed research proposals for the National Science Foundation, the National March of Dimes, the Canada Council and the Human Development Section of NIMH.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00012-06 CFR
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PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Development of Mastery Motivation in Infants

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. J. Yarrow	Chief	CFR, NICHD
	P. M. Viéteze	Head, Mental Retardation	MRRD, NICHD
Other:	R. H. MacTurk	Research Assistant	U. of Maryland
	M. E. McCarthy	Research Assistant	U. of Maryland
	R. P. Klein	Research Psychologist	CFR, NICHD
	S. McQuiston	Research Associate	U. of Illinois - Chicago

COOPERATING UNITS (if any)

Institute for Child Study, University of Maryland

LAB/BRANCH
Child and Family Research Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2.25	PROFESSIONAL: 1.75	OTHER: .50
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The major objective is to investigate the development of mastery motivation in the first year of life. Three aspects of mastery were distinguished: persistence in problem solving, in practicing emerging sensorimotor skills, and in obtaining feedback from the objects. The interrelationships among these components of mastery are being explored, and the origins of mastery and its continuity over time are being studied. The sample includes 75 infants from middle income families. Several methods are being employed--twelve tasks to measure mastery motivation; observation of mother-infant and father-infant interaction in the home; Bayley Scales of Infant Development and parent perception of infant temperament. With regard to the continuity of mastery behaviors, meaningful transformations have been found between 6 and 12 months of age. The interrelations between mastery motivation and cognitive development are complex. Mastery motivation influences cognitive development, and the level of cognitive functioning in turn influences mastery motivation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00013-06 CFR
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) Role of Mother-Infant Relationship in Subsequent Socio-Emotional Development		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: R. P. Klein Research Psychologist CFR, NICHD Other: J. T. D. Suwalsky Research Psychologist CFR, NICHD M. W. Fivel Research Psychologist CFR, NICHD		
COOPERATING UNITS (if any) None		
LAB/BRANCH Child and Family Research Branch		
SECTION		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205		
TOTAL MANYEARS: 1.0	PROFESSIONAL: .75	OTHER: .25
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The objective of this project is to determine whether measures of attachment in infancy are predictive of later adaptation. It is primarily concerned with the relations between the <u>mother-infant relationship</u> , and emotional development during early childhood. Several measures of the <u>mother-infant relationship</u> at the beginning of the infant's second year have been obtained. These infants are being followed through their fifth birthday. For one of the subsamples of this study measures of the father-infant relationship have also been obtained.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-00014-06 CFR
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) Psychological Aspects of Childbearing and the Neonatal Period		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI:	R. Klein	Research Psychologist CFR, NICHD
OTHER:	N. Gist	Research Psychologist CFR, NICHD
COOPERATING UNITS (if any) Department of Obstetrics and Gynecology, The Washington Hospital Center, Washington, D. C.		
LAB/BRANCH Child and Family Research Branch		
SECTION		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Md. 20205		
TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.0	OTHER: 1.0
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords)		
<p> <u>Childbirth</u> involves an interaction of physiology and psychology which may have <u>important consequences</u> for <u>infant development</u>. The objective of this research is to gain understanding of <u>psychological aspects</u> of the <u>childbirth experience</u> and their impact on the well-being of the child, the new parents, and the family unit. A method has been developed for recording the physical state of the woman in labor and medical and social interactions with her. A measure of <u>delivery room events</u> has also been developed. Prenatal and postpartum <u>interviews with parents</u> provide data on their expectations and recollections of the <u>birth process</u> which can be compared with the researcher's observations. Parent's <u>perceptions</u> of the newborn are compared with the researcher's assessment of infant behaviors. </p>		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00015-05 CFR
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PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Parent-Infant Interaction Subsequent to Cesarean Delivery

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	F. A. Pedersen	Research Psychologist	CFR, NICHD
	M. J. Zaslow	Staff Fellow	CFR, NICHD
Other:	R. L. Cain, Jr.	Research Psychologist	CFR, NICHD
	J. T. D. Suwalsky	Research Psychologist	CFR, NICHD
	M. W. Fivel	Research Psychologist	CFR, NICHD
	B. A. Rabinovich	Research Assistant	U. of Maryland

COOPERATING UNITS (if any)

Parent and Child, Childbirth Education Associates, University of Maryland

LAB/BRANCH
Child and Family Research Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.25	OTHER: .25
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this study is to examine the effects of cesarean childbirth on family interaction and on the parent-infant relationship. The sample consists of 46 families with a medically normal, first-born infant, 23 having had a cesarean delivery and 23 a vaginal delivery. When the babies are three months old, and again when they are a year old, two observations are made of mother, father and baby interacting, and one observation is made of mother and baby alone. At each age parents are interviewed and asked to complete a Q-sort assessing their perceptions of their baby's temperament. Cross-sectional and longitudinal analyses will assess differences between the two groups in parents' reports of their experiences during childbirth, in family interaction, and in their adjustment to different birth experiences. In addition, variation within the cesarean birth group will be explored to see whether, for example, the father's presence at a cesarean delivery affects subsequent family interaction.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00016-05 CFR																								
PERIOD COVERED October 1, 1981 to September 30, 1982																										
TITLE OF PROJECT (80 characters or less) The Integration of Child Care and Work Roles																										
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width:100%; border: none;"> <tr> <td style="width:10%; vertical-align: top;">PI:</td> <td style="width:30%;">F. A. Pedersen</td> <td style="width:30%;">Research Psychologist</td> <td style="width:30%;">CFR, NICHD</td> </tr> <tr> <td></td> <td>M. J. Zaslow</td> <td>Staff Fellow</td> <td>CFR, NICHD</td> </tr> <tr> <td style="vertical-align: top;">OTHER:</td> <td>R. L. Cain, Jr.</td> <td>Research Psychologist</td> <td>CFR, NICHD</td> </tr> <tr> <td></td> <td>J. T. D. Suwalsky</td> <td>Research Psychologist</td> <td>CFR, NICHD</td> </tr> <tr> <td></td> <td>M. W. Fivel</td> <td>Research Psychologist</td> <td>CFR, NICHD</td> </tr> <tr> <td></td> <td>B. A. Rabinovich</td> <td>Research Assistant</td> <td>U. of Maryland</td> </tr> </table>			PI:	F. A. Pedersen	Research Psychologist	CFR, NICHD		M. J. Zaslow	Staff Fellow	CFR, NICHD	OTHER:	R. L. Cain, Jr.	Research Psychologist	CFR, NICHD		J. T. D. Suwalsky	Research Psychologist	CFR, NICHD		M. W. Fivel	Research Psychologist	CFR, NICHD		B. A. Rabinovich	Research Assistant	U. of Maryland
PI:	F. A. Pedersen	Research Psychologist	CFR, NICHD																							
	M. J. Zaslow	Staff Fellow	CFR, NICHD																							
OTHER:	R. L. Cain, Jr.	Research Psychologist	CFR, NICHD																							
	J. T. D. Suwalsky	Research Psychologist	CFR, NICHD																							
	M. W. Fivel	Research Psychologist	CFR, NICHD																							
	B. A. Rabinovich	Research Assistant	U. of Maryland																							
COOPERATING UNITS (if any) Parent and Child, Childbirth Education Associates, University of Maryland																										
LAB/BRANCH Child and Family Research Branch																										
SECTION 																										
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205																										
<table style="width:100%; border: none;"> <tr> <td style="width:33%;">TOTAL MANYEARS:</td> <td style="width:33%;">PROFESSIONAL:</td> <td style="width:33%;">OTHER:</td> </tr> <tr> <td style="text-align: center;">2.75</td> <td style="text-align: center;">1.0</td> <td style="text-align: center;">1.75</td> </tr> </table>			TOTAL MANYEARS:	PROFESSIONAL:	OTHER:	2.75	1.0	1.75																		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:																								
2.75	1.0	1.75																								
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																										
SUMMARY OF WORK (200 words or less - underline keywords) <p>The objective of this study is to obtain longitudinal descriptive data on various adaptation patterns which families use to integrate child care and employment in the infant's first year of life. In the first phase of this project a sample consisting of 45 families with a medically normal, first-born infant was studied. These families were classified into 3 groups based on the mothers' workforce participation: those who are full time caregivers, mothers with low rates of outside employment, and mothers with high rates of employment. At 3 months and again at 12 months, two observations are carried out in the families' homes when mother, father and baby are together and one observation is carried out when mother and baby are alone. Parents are interviewed and complete a Q-sort to measure their perceptions of their infant's <u>temperament</u>. Data analysis will consist of cross-sectional and longitudinal <u>comparisons</u> of the different groups. Forty additional families will be studied to focus on the mother's <u>transition</u> to employment.</p>																										

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00019-04 CFR
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PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Mastery Motivation and Social Competence in Down Syndrome Infants

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. J. Yarrow	Chief	CFR, NICHD
	P. M. Vietze	Head, Mental Retardation	MRRD, NICHD
OTHER:	M. E. McCarthy	Research Assistant	U. of Maryland
	R. H. MacTurk	Research Assistant	U. of Maryland
	S. McQuiston	Research Associate	U. of Illinois - Chicago

COOPERATING UNITS (if any)
Institute for Child Study, University of Maryland; Children's Hospital; Children's Brain Research Clinic

LAB/BRANCH
Child and Family Research Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .50	PROFESSIONAL: .25	OTHER: .25
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)
The major objective of this research is to study social competence and mastery motivation in the first year of life of infants with Down syndrome and to examine the relationship between the mother-infant interaction and infant's mastery behaviors. Down syndrome infants are being studied longitudinally at 3, 6 and 8 months, and a cross-sectional sample is being studied at 12 months of age. Mastery motivation is being assessed using 12 tasks developed in this laboratory. An observational system which preserves the sequence and continuity of the transactions between mother and infant is being employed to examine the mother-infant interaction. In addition, the relationship between the infants' social and mastery behaviors and specific cognitive, and temperamental variables is being examined. Infants with Down syndrome show patterns similar to normal infants in the distribution of visual attention, exploratory behavior and goal-directed behaviors in the second half of the first year; by the end of the first year, they show less persistence in and success on problem solving tasks. Patterns of mother infant interaction for the Down syndrome children differ from those of normal children.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-HD-01100-03
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) A Follow-up Study of Mastery Motivation		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI:	L. J. Yarrow D. J. Messer	Chief, CFR Branch Visiting Fellow
		CFR, NICHD CFR, NICHD
OTHER:	C. W. Rahn M. E. McCarthy R. H. MacTurk	Research Psychologist Research Assistant Research Assistant
		CFR, NICHD U. of Maryland U. of Maryland
COOPERATING UNITS (if any) Institute of Child Study, University of Maryland		
LAB/BRANCH Child and Family Research Branch		
SECTION		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.0	OTHER: 1.0
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords)		
<p>In this longitudinal study of the development of <u>mastery motivation</u>, the goals are to determine whether mastery motivation in <u>infancy</u> is predictive of later mastery behavior and to determine the role of <u>early parent-infant interaction</u> in the development of mastery behavior at 2 1/2 years. The relationships between <u>cognitive functions</u> and mastery motivation during the <u>preschool years</u> is also being studied. An important part of this study has been the development of methods to assess similar aspects of mastery at 2 1/2 years as were studied at 6 and 12 months of age. Data have been collected in a focused play session, an observation of the infant's free play with the mastery toys, observation of the children's mastery of a learning problem, and a brief observation of mother-child interaction with another set of toys. Data on cognitive development have been obtained by the McCarthy scales. Preliminary analyses suggest that visual attention-ponents of mastery.</p>		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 HD 01101-01 CFR

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Naturally-Occurring Separations between Mother and Infant During the First Year of Life

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	J. T. D. Suwalsky	Research Psychologist	CFR, NICHD
	M. J. Zaslow	Staff Fellow	CFR, NICHD
Other:	R. P. Klein	Research Psychologist	CFR, NICHD
	B. A. Rabinovich	Research Assistant	U. of Maryland
	N. F. Gist	Research Psychologist	CFR, NICHD

COOPERATING UNITS (if any)

Institute of Child Study, University of Maryland

LAB/BRANCH

Child and Family Research Branch

SECTION

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:

1.5

PROFESSIONAL:

1.0

OTHER:

.5

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to identify and differentiate variables believed to mediate the effects of naturally-occurring non-traumatic separations of mother and infant during the first twelve months and to relate these variables to outcome measures of social-emotional functioning in the second year. The variables being studied are a) aspects of the separations themselves, b) characteristics of the substitute care provided, and c) contextual factors such as the reason for the separation and maternal attitudes about it. Data about separations, alternative care arrangements and maternal attitudes were obtained from 144 mothers during their baby's first year by interview. When the babies were approximately 15 months old, measures of the baby's response to strangers and attachment to mother were obtained in a standardized laboratory procedure. Analyses will relate aspects of separations, substitute care and contextual factor to outcome measures of social-emotional functioning.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 01102-01 CFR
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PERIOD COVERED
December 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)

Behavioral Correlates of Endocrine Disorders in Children

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Robert P. Klein	Research Psychologist	CFRB/NICHD
Other: William Sonis Charles Rahn Jerome Blue	Medical Staff Fellow Research Psychologist Staff Fellow	NPMB/NICHD CFRB/NICHD LDP/NIMH

COOPERATING UNITS (if any)

Florence Comite, M.D., DEB/NICHD; Barry Bercu, M.D., NPMB/NICHD; Judy Levine, M.D.
DEB/NICHD

LAB/BRANCH
Child and Family Research Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.2	PROFESSIONAL: 1.0	OTHER: .2
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project focuses on the psychiatric, psychological and social correlates of endocrine disorders of growth, development and maturation in children ages 4 to 16. The disorders being studied include precocious puberty, Turners Syndrome, short stature and delayed adolescence. As a first step we are extensively studying many disorders using a well standardized parental report screening instrument, the Child Behavior Check List (CBCL). Raw and normalized scale scores are obtained for the child's social competency and behavior problems. Data will be analyzed on several levels. On the simplest level, separate comparisons, will be made of the children with each disorder and children from the sample used to standardize the CBCL matched on sex, age, race and SES. A second level uses the various disorders as comparison groups for each other, thus allowing us to control for such factors as hospitalization and unusual physical appearance. A third level would use each child as his own control to assess the effects of treatment, obtaining measures before and after treatment. The results from these analyses can, in turn, suggest leads for more intensive study of specific aspects of disturbed functioning in children with these disorders.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 HD 01103-01 CFR

PERIOD COVERED

May 1, 1982 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Sleep Ontogeny in Children with Precocious Puberty

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. William Sonis, M.D.

Medical Staff Fellow

CFRB, NICHD

COOPERATING UNITS (if any)

Wallace Mendelson, M.D., NIMH; Florence Comite, M.D., DEB, NICHD

LAB/BRANCH

Child and Family Research Branch

SECTION

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:

.5

PROFESSIONAL:

.5

OTHER:

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS

(b) HUMAN TISSUES

(c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Children with precocious puberty have dysphasic sexual development, usually secondary to early maturation of the hypothalamic-pituitary axis. The object of this study is to examine the sleep architecture of these children compared to age and sex matched normal controls, to see if CNS maturation parallels chronological age or sexual maturation.

1982 ANNUAL REPORT
Pregnancy Research Branch

SUMMARY

<u>Project Numbers</u>	<u>Project Title</u>	<u>Principal Investigator</u>
Z01 HD 00026-07 PR	Fertilization and Activation of Development in Mammals.....	B. Gulyas
Z01 HD 00031-09 PR	Hormonal Interrelationships Between Fetus, Mother and Placenta in Primates.....	G. Hodgen
Z01 HD 00045-07 PR	Regulation of Folliculogenesis in the Monkey.....	G. Hodgen
Z01 HD 00168-06 PR	Ovarian Xenobiotic Metabolism and Oocyte Toxicity.....	D. Mattison
Z01 HD 00900-04 PR	Factors Regulating Estrogen and Progesterone Receptors in Monkey Endometrium in the Fertile Menstrual Cycle.....	G. Hodgen
Z01 HD 00901-04 PR	Endocrine Assays Laboratory.....	W. Nixon
Z01 HD 00907-03 PR	Reproductive Toxicity of Drugs.....	D. Mattison
Z01 HD 00908-03 PR	Genetics of Ovarian Failure.....	D. Mattison
Z01 HD 00909-03 PR	Effects of Ethanol on the Mother and the Fetus.....	A. Mukherjee
Z01 HD 00910-03 PR	Role of Uteroglobin and Transglutaminase in Reproduction.....	A. Mukherjee
Z01 HD 00912-03 PR	Gene Regulation and Cellular Differentiation.....	J. Chou
Z01 HD 00913-03 PR	Primate Models for In Vitro Fertilization and Alternatives.....	G. Hodgen
Z01 HD 00914-03 PR	Fallopian Tube Dysfunction and Endometriosis.....	G. Hodgen
Z01 HD 00916-02 PR	Studies of Corpus Luteum Function in the Cycling and Pregnant Monkey: <u>Relaxin Secretion</u>	W. Nixon
Z01 HD 00917-02 PR	Gene Transfer by Chromosomes, Lipochromosomes and Liposome Encapsulated DNA.....	A. Mukherjee
Z01 HD 00918-01 PR	Mechanism of Suppression of Immune Response to Paternal Transplantation Antigens by Pregnant Female.....	K. Ozato
Z01 HD 00919-01 PR	Monoclonal Antibodies Which Detect Antigens of Neuro-endocrine Tissue.....	K. Ozato
Z01 HD 00920-01 PR	Mouse Transplantation Antigeny (H-2) Genes: DNA Sequence Basis for Immunological Parameters Associated with H-2 Antigens.....	K. Ozato
Z01 HD 00921-01 PR	Fetal Diagnosis and Therapeutics.....	D. Mattison
Z01 HD 00922-01 PR	Nuclear Transfer in Mammalian Oocytes.....	B. Gulyas

ANNUAL REPORT
of the
Pregnancy Research Branch
National Institute of Child Health and Human Development
October 1, 1981 through September 30, 1982

SUMMARY

The current research program of the Pregnancy Research Branch focuses upon the physiology of gestation (including genetic and developmental factors which contribute to perinatal fetal and maternal morbidity and mortality), fertility regulation, toxicological aspects of ovarian function, as well as fertilization and implantation. The Branch trains Associates and Visiting Fellows in laboratory and clinical investigation by participation in the combined program in Reproductive Endocrinology that has been established with the Armed Forces Institute, specifically for career development in obstetrics and gynecology. Also, the combined program with NIAMDD is available to Clinical Associates interested in Endocrinology. In addition, the Pregnancy Research Branch has received approval jointly with the Department of Obstetrics and Gynecology, Georgetown University to establish sub-specialty certified Fellowships in Maternal-Fetal Medicine and Gynecologic Endocrinology and Infertility.

The investigations of hormonal regulation and gene expression in placenta and liver are essential for an understanding of fetal development and embryogenesis. The study of the control of gene expression of alkaline phosphatase, hCG, PS β G and AFP is of importance because these proteins are derepressed in many tumors. Ectopic production of these fetal proteins may serve as an early signal of malignant transformation. The establishment of human placental cells and rat fetal liver cells which approximate normal placental and liver cells in vivo respectively should help us to elucidate the control mechanisms for the synthesis of these proteins.

We have identified and cloned two DNA sequences encoding mouse major histocompatibility antigens (H-2) from BALB/c genomic DNA. DNA sequences of the 2 genes agreed with available amino acid sequences for H-2L^d and H-2D^d antigens. When cloned DNA was introduced into mouse L cells by DNA mediated gene transfer, new H-2 antigens appeared which carried H-2L^d or H-2D^d determinants as detected by batteries of monoclonal antibodies of defined specificity. Efforts will be focused this year for establishing the DNA sequence basis for various immunological parameters of H-2 antigen. This will be carried out with hybrid genes prepared by exchanging various part of H-2L^d and H-2D^d gene. In order to shed light into the molecular evolution of H-2 genes, H-2 genes of other mutant and wild mice will be examined.

We have prepared more than 25 hybridoma clones which detect antigens in anterior or posterior pituitary gland. The clones which detected posterior pituitary also reacted with hypothalamus tissue preparation. Immunoblot analysis indicates that most of antigens are of MW about 12000 daltons similar to neurophysins. We wish to continue to increase our library of monoclonal antibodies. Using established monoclonal antibodies, extensive molecular identification will be carried out, relying mainly on immunoblot technique. We also wish to address questions of developmental nature as to the time and localization of the onset of antigen synthesis. We have found a major idio type in anti-H-2L^d humoral response by a xeno-anti-idiotypic antibody raised against a monoclonal anti-H-

2L^d antibody. When idiotypic was injected into syngeneic mouse, they readily mounted anti-idiotypic indicating the presence of idiotypic-anti-idiotypic network regulation. BALB/c H-2^{dm2} females will be mated with BALB/c males and sera from pregnant or multiparous females will be examined for the presence of anti-idiotypic antibodies against the major idiotypic.

We have used SV40 DNA as well as AKR MuLV gene integrated into mouse cell. The amount of DNA entrapped in liposomes was dependent on the input DNA concentration and lipid composition. DNA remained intact after liposome encapsulation and was resistant to deoxyribonuclease digestion. Negatively-charged liposomes containing phosphatidyl-serine were more effective in DNA transfer and expression than neutral liposomes. Plaque formation was stimulated 10-50 fold by post-treatment with glycerol. We believe liposomes can efficiently introduce genes into desired cells.

We previously reported experimental evidence that uteroglobin (UG) in conjunction with transglutaminase (TG) can mask the antigenicity of implanting rabbit embryos as well as epididymal sperm. Although the male gametes as well as the implanting embryos express antigens which are different from the female host, they nonetheless do not sensitize the females immunologically. Our proposed hypothesis that uteroglobin and transglutaminase may be instrumental in masking the antigenicity of the male gametes and early embryos required experimental evidence. The presence of a uteroglobin-sperm surface protein complex may provide such an evidence.

While conducting laboratory studies on the kinetics of ethanol transfer across the placenta to fetal monkeys, we observed that 10-15 minutes after ethanol was administered to the mother, the vasculature of the umbilical cord collapsed. Subsequent recovery of umbilical function from this flaccid state occurred during the next hour. Ethanol-induced transient impairment of umbilical circulation and resultant fetal hypoxia may lead to irreversible brain damage. The sticking interruption of feto-placental circulation may explain one of the mechanisms of mental retardation, a frequent manifestation in children afflicted with Fetal Alcohol Syndrome.

Relaxin secretion is another function of the corpus luteum. The role of relaxin in the reproductive process is under active investigation to determine its source, possible stimulants to secretion and tropic effects of this hormone at traditional as well as other possible target tissues. Although a role for relaxin at parturition has been propounded for a number of species, the lack of a pre-parturition rise in primates brings that role into question.

Four families with heritable premature ovarian failure have been identified. Two families have been studied in some detail and no known immunological or genetic abnormalities previously associated with premature ovarian failure have been identified. The two additional families are presently being investigated. The ultimate event of reproductive senescence in the female is the depletion of oocytes from the ovary. The age at which the ovary is depleted of oocytes depends in part upon the initial complement of oocytes, the rate of recruitment and atresia, as well as the effects of exposure to ovotoxins. Characterization of the genetics of oocyte loss in mice may provide insight into the biological nature of these processes. Additionally, these studies may also help clarify the interrelationship between oocyte toxicity and oocyte loss. Previous experiments have demonstrated that drugs which produce oocyte destruction in humans also

destroy oocytes in rodents. In spite of the obvious utility of the experimental animal models there appear to be differences in the details of the ovarian responses to alkylating agents. Reasons for differential follicle sensitivity, with primordial follicles the most sensitive in rodents, remains elusive. Further observation of patients treated with cyclophosphamide demonstrated rapid onset of amenorrhea, with elevated gonadotropins and decreased ovarian steroid production in women older than 25. This decrease in ovarian steroid production is paralleled by a decrease in ovarian size as measured by ultrasound, suggesting toxicity to growing and preovulatory follicles. Further research will explore in greater detail the gonadal and reproductive toxicity of cyclophosphamide and other antitumor agents to determine effects on ovarian and pituitary function, as well as follicle susceptibility. Previous electron microscopic investigations in this laboratory have demonstrated that oocyte destruction can occur in the absence of identifiable morphological alterations of granulosa cells. One major accomplishment of the past year has been verification of our previous observations suggesting that the ovary is fully capable of metabolizing xenobiotics like benzo(a)pyrene to ovotoxic products. These experiments provide the basis for elucidation of the mechanism of action of one class of reproductive toxins.

A technique was developed for fusing oocytes, which in turn are capable of continuing development to the 14 somite stage. The fusion technique appears promising as a means of introducing donor nucleus in future research. Enucleation of mouse eggs was tested under two different conditions, a) removing both pronuclei of fertilized eggs or, b) removing a single pronucleus from parthenogenetically activated eggs. Such fusion products can develop into blastocysts and when transferred to foster mothers can continue development, at least up to 14 somite stage. During the past year this project focused upon the physiological and immunological aspects of zona specific antigens and their possible use in fertility control using monkeys as a model. The objective of the project was to immunize monkeys with isolated pig zonae and evaluate 1) its antifertility effect, 2) long term effects on the ovaries, 3) reversibility of antifertility and 4) effects on cyclicity and hormonal patterns.

The results indicate that monkeys can be immunized against heterogenous zonae pellucidae. However, initial high titers of circulating antibodies alone are not enough to render the monkeys infertile because half of the monkeys conceived just at a time maximal antibody titers were reached, suggesting that it can not reach or alter the zona of mature oocytes. The available antizona antiserum will be further characterized with respect to its ability to 1) cross react with zonae of heterologous species, 2) harden the zona in the mouse, 3) interact with sperm-egg binding, 4) in vitro fertilization in heterologous and possibly homologous species, 5) utilization in passive immunization.

The physiological control of ovarian function and endocrine regulation during the reproductive cycle in pregnancy was extensively analyzed in the monkey as a model for understanding of ovarian function in the primate; these studies continue. The regulation of ovarian folliculogenesis, and selection of the dominant ovarian follicle, was examined during the primate ovarian cycle. Circulating patterns of gonadotropin and ovarian steroids were measured by radioimmunoassay before the after manipulations that included follicle cautery, luteectomy, and hemiovariectomy; during the monkey menstrual cycle. In addition to these studies on follicle growth during the non-fertile menstrual cycle, the resumption of follicle growth was investigated in these animals during the puerperium. The

relationship between ovarian function and the conceptus, as well as the cessation of follicle growth during pregnancy, were also studied during the fertile menstrual cycle. Among newer interests is relaxin. Current studies are aimed at understanding its effects on ovarian function.

Recently, it was found that charcoal-treated bovine and porcine follicular fluid (PFF1) reduced peripheral plasma FSH levels, with little alteration in LH levels, in gonadectomized rats and in cycling female rats and monkeys. The data suggested the presence of a nonsteroidal substance (inhibin) in follicular fluid thought to be responsible for regulation of FSH secretion. Administration of porcine follicular fluid to suppress circulating FSH offers a convenient, novel system for evaluating the actions of FSH during the ovarian cycle. In current studies we are testing the effects of PFF1 administration during the first half of the menstrual cycle on follicle development in the rhesus monkey. The goal of this research is to test the hypothesis that the formation and steroidogenic activity of luteal tissue may be impaired, when the corpus luteum originates from a developing follicle exposed to less-than-normal FSH. Even greater and more lengthy suppression of serum FSH is associated with anovulation. A related finding indicates that FSH may induce inhibin secretion which in turn regulates selection of the dominant follicle. When hMG is used to enhance in vitro fertilization, spontaneous LH surges are blocked. This may derive from excess FSH stimulation.

The major cause of human infertility in the U.S.A. is tubal dysfunction. Endometriosis and other causes of failure to achieve satisfactory gamete transport are major contributing factors. We sought to examine how these infertilities arise and how to better treat them medicinally and surgically. The cause of infertility when endometrial tissue grows ectopically is unknown; even its hormonal support is poorly understood. We studied: 1) the role of estrogens and progesterone in the maintenance of ectopic endometrial plaques; and 2) the effect of ectopic endometrium on ovum and sperm transport. Current projects are aimed at determining if ovum pick-up at ovulation and tubal transport of both egg and sperm are inhibited by ectopic endometrium. Also, we are evaluating GnRH analogues as a preferred treatment for endometriosis. Preliminary results using individualized, intermittent regimens are very promising.

As illustrated by the studies summarized in this report, the investigators within the Pregnancy Research Branch have developed a broad range of studies on normal processes and disorders which affect fertility and gestation. A variety of animal models and clinical interests are being pursued with the expectation that useful information will be derived about the basic causes and optimal treatment of disorders adversely affecting the reproductive process, especially pregnancy.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00026-07 PR						
PERIOD COVERED October 1, 1981 to September 30, 1982								
TITLE OF PROJECT (80 characters or less) Fertilization and Activation of Development in Mammals								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">P.I.: Bela J. Gulyas</td> <td style="width: 33%;">Senior Investigator</td> <td style="width: 33%;">PRB, NICHD</td> </tr> <tr> <td>Other: Lydia C. Yuan</td> <td>Chemist-Technician</td> <td>PRB, NICHD</td> </tr> </table>			P.I.: Bela J. Gulyas	Senior Investigator	PRB, NICHD	Other: Lydia C. Yuan	Chemist-Technician	PRB, NICHD
P.I.: Bela J. Gulyas	Senior Investigator	PRB, NICHD						
Other: Lydia C. Yuan	Chemist-Technician	PRB, NICHD						
COOPERATING UNITS (if any) R.B.L. Gwatkin, Department of Obstetrics and Gynecology; McMaster University, Hamilton, Ontario, Canada								
LAB/BRANCH Pregnancy Research Branch								
SECTION Section on Endocrinology								
INSTITUTE AND LOCATION NICHD, Bethesda, MD 20205								
TOTAL MANYEARS: <div style="text-align: center;">2</div>	PROFESSIONAL: <div style="text-align: center;">1</div>	OTHER: <div style="text-align: center;">1</div>						
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS								
SUMMARY OF WORK (200 words or less - underline keywords) To study the function of <u>zona pellucida</u> specific antigens in the initial sperm-egg interaction and their possible role in <u>fertility control</u> , cynomolgus <u>monkeys</u> were immunized with porcine zonae pellucidae. To assess the levels of antibody titers, a simple and rapid, <u>solid-phase RIA</u> was developed utilizing ¹²⁵ I protein A. The study demonstrated that monkeys can be immunized against heterologous zonae and rendered infertile. Indications are that the antibody can not reach the zonae of large antral follicles since several monkeys became pregnant just at the time circulating titers of antizona antibodies reached maximal. Instead, the antibody may interfere with progression of primordial and small primary follicles to antral follicles. Infertility was <u>reversible</u> in some of the monkeys, but they had still births to otherwise normal babies. The oocyte population was considerably reduced by atresia by the end of 18 months of the study.								

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00031-09 PR												
PERIOD COVERED October 1, 1981 to September 30, 1982														
TITLE OF PROJECT (80 characters or less) Hormonal Interrelationships Between Fetus, Mother and Placenta in Primates														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0" data-bbox="59 499 1377 604"> <tr> <td>P.I.:</td> <td>Gary D. Hodgen</td> <td>Chief</td> <td>PRB, NICHD</td> </tr> <tr> <td>Other:</td> <td>Robert F. Williams</td> <td>Senior Staff Fellow</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>David L. Healy</td> <td>Guest Scientist</td> <td>PRB, NICHD</td> </tr> </table>			P.I.:	Gary D. Hodgen	Chief	PRB, NICHD	Other:	Robert F. Williams	Senior Staff Fellow	PRB, NICHD		David L. Healy	Guest Scientist	PRB, NICHD
P.I.:	Gary D. Hodgen	Chief	PRB, NICHD											
Other:	Robert F. Williams	Senior Staff Fellow	PRB, NICHD											
	David L. Healy	Guest Scientist	PRB, NICHD											
COOPERATING UNITS (if any) None														
LAB/BRANCH Pregnancy Research Branch														
SECTION Section on Endocrinology														
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205														
TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.5	OTHER:												
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS														
SUMMARY OF WORK (200 words or less - underline keywords) Over the past 12 years, a continuum of studies has been directed at understanding the <u>hormoneal interrelationships</u> between the <u>fetal, placental and maternal compartments</u> . Most of these studies have utilized <u>primate models</u> , where the similarities to equivalent events in human pregnancies are most extensive. During previous years, we concluded a series of experiments which employed <u>fetal hypophysectomy</u> in rhesus monkeys to establish the importance of fetal hypophyseal secretion for <u>gonadal development in utero</u> ; particular attention was given to <u>ovarian and testicular development</u> . During the past year we have demonstrated a synergistic action of fetoplacental estrogens and progesterone in regulating maternal prolactin secretion, and we have developed a fetal cannulation procedure which allows for repeated sampling of fetal blood for determining the relationship between pulsatile LH and FSH secretion and gonadal differentiation. To this we have added studies that test GnRH responsiveness of the term fetus versus neonate at one week.														

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00045-07 PR																																								
PERIOD COVERED October 1, 1981 to September 30, 1982																																										
TITLE OF PROJECT (80 characters or less) Regulation of Folliculogenesis in the Monkey																																										
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT																																										
<table style="width:100%; border: none;"> <tr> <td style="width:33%;">P.I.:</td> <td style="width:33%;">Gary D. Hodgen</td> <td style="width:33%;">Chief</td> <td style="width:33%;">PRB, NICHD</td> </tr> <tr> <td>Other:</td> <td>Wilbert E. Nixon</td> <td>Senior Investigator</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>Robert F. Williams</td> <td>Senior Staff Fellow</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>Gere S. diZerega</td> <td>Clinical Associate</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>Edward L. Marut</td> <td>Clinical Associate</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>Lawrence B. Werlin</td> <td>Clinical Associate</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>Bryan D. Cowan</td> <td>Guest Scientist</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>Robert Stillman</td> <td>Guest Scientist</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>Robert Schenken</td> <td>Guest Scientist</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>Victoria Sopelak</td> <td>Guest Scientist</td> <td>PRB, NICHD</td> </tr> </table>			P.I.:	Gary D. Hodgen	Chief	PRB, NICHD	Other:	Wilbert E. Nixon	Senior Investigator	PRB, NICHD		Robert F. Williams	Senior Staff Fellow	PRB, NICHD		Gere S. diZerega	Clinical Associate	PRB, NICHD		Edward L. Marut	Clinical Associate	PRB, NICHD		Lawrence B. Werlin	Clinical Associate	PRB, NICHD		Bryan D. Cowan	Guest Scientist	PRB, NICHD		Robert Stillman	Guest Scientist	PRB, NICHD		Robert Schenken	Guest Scientist	PRB, NICHD		Victoria Sopelak	Guest Scientist	PRB, NICHD
P.I.:	Gary D. Hodgen	Chief	PRB, NICHD																																							
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COOPERATING UNITS (if any)																																										
LAB/BRANCH Pregnancy Research Branch																																										
SECTION Section on Endocrinology																																										
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205																																										
TOTAL MANYEARS: 4	PROFESSIONAL: 2	OTHER: 2																																								
CHECK APPROPRIATE BOX(ES)																																										
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER																																										
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																																										
SUMMARY OF WORK (200 words or less - underline keywords)																																										
<p>Endocrine factors contributing to the regulation of <u>folliculogenesis</u> (selection of the <u>dominant follicle</u>) during the <u>primate ovarian cycle</u> were examined in two <u>non-human primate models</u>, the <u>rhesus monkey</u>, and the <u>cynomolgus monkey</u>. Circulating patterns of <u>gonadotropins</u> and ovarian steroids (<u>estradiol</u> and <u>progesterone</u>) were monitored by <u>radioimmunoassay</u> before and after <u>follicle cautery</u>, <u>luteectomy</u> and during the <u>menstrual cycle</u> in monkeys. In addition to examining <u>follicle growth</u> during the <u>nonfertile menstrual cycle</u>, the <u>resumption of follicle growth</u> was studied during the <u>puerperium</u>. Ovary <u>conceptus interrelationships</u>, as well as the <u>cessation of follicle growth in pregnancy</u> were studied during the <u>fertile menstrual cycle</u>. Salient findings include: 1) usefulness of the <u>cynomolgus monkey</u> as <u>alternative non-human primate model</u>, 2) <u>asymmetrical function</u> of the two ovaries during the menstrual cycle, 3) evidence that the <u>dominant follicle</u> is selected during the first of the menstrual cycle, 4) onset of <u>asymmetrical ovarian function</u> prior to the onset of ovulatory cycles in juvenile monkeys, and 5) the enhanced biological activity of LH associated with the onset of the first ovulatory cycles and at mid-cycle in adult ovulatory monkeys.</p>																																										

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00168-06 PR																								
PERIOD COVERED October 1, 1981 to September 30, 1982																										
TITLE OF PROJECT (80 characters or less) Ovarian Xenobiotic Metabolism and Oocyte Toxicity																										
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0"> <tr> <td>P.I.:</td> <td>Donald R. Mattison</td> <td>Medical Officer</td> <td>PRB, NICHD</td> </tr> <tr> <td>Other:</td> <td>Maria Nightingale</td> <td>Chemist</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>Donna Kuroda</td> <td>Guest Scientist</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>Ken Takizawa</td> <td>Visiting Fellow</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>Lucy Chang</td> <td>Biological Aide</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>Andre Wagner</td> <td>Biological Aide</td> <td>PRB, NICHD</td> </tr> </table>			P.I.:	Donald R. Mattison	Medical Officer	PRB, NICHD	Other:	Maria Nightingale	Chemist	PRB, NICHD		Donna Kuroda	Guest Scientist	PRB, NICHD		Ken Takizawa	Visiting Fellow	PRB, NICHD		Lucy Chang	Biological Aide	PRB, NICHD		Andre Wagner	Biological Aide	PRB, NICHD
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	Lucy Chang	Biological Aide	PRB, NICHD																							
	Andre Wagner	Biological Aide	PRB, NICHD																							
COOPERATING UNITS (if any) Dr. Jerina, Chief OMS, LBC, NIAMDD; Nathaniel White, Statistician, NIEHS; David Longfellow, Asst. Chief CPCB, NCI; Carol Henry, Director, Dept. Exptl. Oncology, Microbiological Associates; James Felton, Lawrence-Livermore Laboratories; Kenji Shiromizu, University of Tokyo																										
LAB/BRANCH Pregnancy Research Branch																										
SECTION Section on Endocrinology																										
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205																										
TOTAL MANYEARS: 3.5	PROFESSIONAL: 1.5	OTHER: 2																								
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																										
SUMMARY OF WORK (200 words or less - underline keywords) <p>Certain <u>polycyclic aromatic hydrocarbons</u> are <u>metabolized by ovarian enzymes</u> to reactive products which destroy oocytes. <u>Intraovarian injection of benzo(a)pyrene</u> or derivatives of benzo(a)pyrene also produces oocyte destruction, suggesting that ovarian metabolism is responsible for the observed <u>ovotoxicity</u>. Murine strain differences in sensitivity to ovotoxins disappear when mice are treated with a putative ultimate ovotoxin the <u>7,8-dihydrodiol-9,10-epoxide</u> metabolite of benzo(a)pyrene by intraovarian injection. This suggests that differences in <u>metabolic activation</u> may be a major determinant in strain and species differences in response to ovotoxins. <u>Oocyte destruction</u> by polycyclic aromatic hydrocarbons is <u>inherited as a polygenic trait</u> and is not linked to the aromatic hydrocarbon responsiveness locus (Ah locus). Characterization of <u>benzo(a)pyrene metabolites</u> produced by ovarian enzymes suggests that metabolism in the 7,8,9,10 region may reflect more accurately the ability of the ovary to activate the parent compound to ovotoxic products.</p>																										

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00900-04 PR
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PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Factors Regulating Estrogen and Progesterone Receptors in Monkey Endometrium
in the Fertile Menstrual Cycle

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER
PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	G.D. Hodgen	Chief	PRB, NICHD
Other:	B. Kreitmann	Guest Scientist	PRB, NICHD
	D. Healy	Guest Scientist	PRB, NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Pregnancy Research Branch

SECTION
Section on Endocrinology

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 3	PROFESSIONAL: 2	OTHER: 1
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CHECK APPROPRIATE BOX(ES)
 (a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER
 (a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)
 Appropriate methods for repeated surgical collection of endometrial tissue from monkeys and characterization of cytosol and nuclear estrogen and progesterone receptors have been developed. Equilibrium dissociation constants of estradiol and progesterone were $2.1 \times 10^{-10}M$ and $3.6 \times 10^{-9}M$, respectively. When estrogen or estrogen + progesterone replacement therapy was given to castrate monkeys, we found that progesterone receptor synthesis was induced by estrogens. Further, in the fertile menstrual cycle, progesterone secretion from the corpus luteum preserved the endometrium, induced a shift toward enhanced nuclear receptors for estrone.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00901-04 PR												
PERIOD COVERED October 1, 1981 to September 30, 1982														
TITLE OF PROJECT (80 characters or less) Endocrine Assays Laboratory														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0" data-bbox="80 473 1172 584"> <tr> <td>P.I.:</td> <td>Wilbert E. Nixon</td> <td>Senior Investigator</td> <td>PRB, NICHD</td> </tr> <tr> <td>Other:</td> <td>Rudolph Reid</td> <td>Technician</td> <td>PRB, NICHD</td> </tr> <tr> <td></td> <td>Terrance Stradford</td> <td>Stay-in-School</td> <td>PRB, NICHD</td> </tr> </table>			P.I.:	Wilbert E. Nixon	Senior Investigator	PRB, NICHD	Other:	Rudolph Reid	Technician	PRB, NICHD		Terrance Stradford	Stay-in-School	PRB, NICHD
P.I.:	Wilbert E. Nixon	Senior Investigator	PRB, NICHD											
Other:	Rudolph Reid	Technician	PRB, NICHD											
	Terrance Stradford	Stay-in-School	PRB, NICHD											
COOPERATING UNITS (if any) None														
LAB/BRANCH Pregnancy Research Branch														
SECTION Section on Endocrinology														
INSTITUTE AND LOCATION NICHD, Bethesda, MD 20205														
TOTAL MANYEARS: 1	PROFESSIONAL: .2	OTHER: .8												
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS														
SUMMARY OF WORK (200 words or less - underline keywords) This laboratory has provided a number of services to Pregnancy Research Branch and other NICHD investigators. The Endocrine Assays Laboratory generated, titered and distributed <u>sheep anti-rabbit gamma globulin sera</u> (second antibody) to NICHD Intramural Investigators, mostly in PRB, ERRB and DEB. Rigid quality control and efficient harvesting procedures were combined to provide a high quality reagent at a fraction of the commercial cost. <u>Radioimmunoassay</u> procedures for <u>polypeptide</u> and <u>steroid hormones</u> of reproductive interest have been maintained and utilized for research investigations. <u>Teaching</u> of radioimmunoassay <u>methodology</u> for polypeptide and steroid hormones has been provided as required by on-campus and local off-campus requests. In addition, <u>antisera</u> to steroid hormones were provided off-campus investigators.														

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00907-03 PR																		
PERIOD COVERED October 1, 1981 to September 30, 1982																				
TITLE OF PROJECT (80 characters or less) Reproductive Toxicity of Drugs																				
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width:100%; border: none;"> <tr> <td style="width:33%;">P.I.: Donald R. Mattison</td> <td style="width:33%;">Medical Officer</td> <td style="width:33%;">PRB, NICHD</td> </tr> <tr> <td>Other: Maria Nightingale</td> <td>Chemist</td> <td>PRB, NICHD</td> </tr> <tr> <td>Ken Takizawa</td> <td>Visiting Fellow</td> <td>PRB, NICHD</td> </tr> <tr> <td>Doris Pfeiffer</td> <td>Guest Scientist</td> <td>PRB, NICHD</td> </tr> <tr> <td>Lucy Chang</td> <td>Biological Aide</td> <td>PRB, NICHD</td> </tr> <tr> <td>Nanette McAtee</td> <td>Nurse</td> <td>CC, NIH</td> </tr> </table>			P.I.: Donald R. Mattison	Medical Officer	PRB, NICHD	Other: Maria Nightingale	Chemist	PRB, NICHD	Ken Takizawa	Visiting Fellow	PRB, NICHD	Doris Pfeiffer	Guest Scientist	PRB, NICHD	Lucy Chang	Biological Aide	PRB, NICHD	Nanette McAtee	Nurse	CC, NIH
P.I.: Donald R. Mattison	Medical Officer	PRB, NICHD																		
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Lucy Chang	Biological Aide	PRB, NICHD																		
Nanette McAtee	Nurse	CC, NIH																		
COOPERATING UNITS (if any) Snorri Thorgeirsson, Head, Biochem. Pharm. Sect. NCI; Anthony Fauci, Head, Clin. Physiol. Sect., Lab. Clin. Invest., NIAIDD; Susan Fabro, Head, Pharm. & Exper. Thera. Sect., NCI; Thomas Shawker, Chief, Ultrasound, CC.																				
LAB/BRANCH Pregnancy Research Branch																				
SECTION Section on Endocrinology																				
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205																				
TOTAL MANYEARS: 2.5	PROFESSIONAL: 1	OTHER: 1.5																		
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input checked="" type="checkbox"/> (a2) INTERVIEWS																				
SUMMARY OF WORK (200 words or less - underline keywords) <u>Cyclophosphamide destroys oocytes in rodents and humans producing early ovarian failure.</u> Although rodents are useful models for exploring mechanisms of ovarian toxicity, their differential follicular sensitivity appears different from that observed in women. Recent observations on young women treated with cyclophosphamide confirms previous observations of an inverse <u>age dependent sensitivity</u> to ovotoxins.																				

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00908-03 PR
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) Genetics of Ovarian Failure		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
P.I.: Donald R. Mattison Other: Joseph D. Schulman Y.T. Chen Lucy Chang	Medical Officer Medical Officer Clinical Associate Biological Aide	PRB, NICHD NPMB, NICHD DPB, NICHD PRB, NICHD
COOPERATING UNITS (if any) Carol Henry, Director, Dept. Exptl. Oncology, Microbiological Associates; Nathaniel White, Statistician, NIEHS; Blanch McFarland, Biomedical Mathematical Modeling Consultant; Beverley White, Senior Investigator, NIAMDD		
LAB/BRANCH Pregnancy Research Branch		
SECTION		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205		
TOTAL MANYEARS: 1.0	PROFESSIONAL: 0.3	OTHER: 0.7
CHECK APPROPRIATE BOX(ES)		
<input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input checked="" type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords)		
<p>Four families with <u>heritable forms of premature ovarian failure</u> are being investigated. At the present time no previously identified etiology of premature ovarian failure has been found in these women. Prenatal <u>galactose</u> treatment during the first half of pregnancy decreases <u>oocyte number</u> in the <u>rat</u>. This suggests that <u>primordial germ cell proliferation or migration</u>, or <u>oogonial proliferation</u> are adversely effected by galactose. This rodent system represents a useful model for exploration of the mechanism of premature ovarian failure observed in women with galactosemia.</p>		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00909-03 PR
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) Effects of Ethanol on the Mother and the Fetus		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Anil B. Mukherjee Chief, Section on Molecular PRB, NICHD and Developmental Genetics		
COOPERATING UNITS (if any) Dr. Gary Hodgen, Chief, PRB, NICHD		
LAB/BRANCH Pregnancy Research Branch		
SECTION Section on Molecular and Developmental Genetics		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205		
TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.5	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) When moderate amounts of <u>ethanol</u> administered intravenously to pregnant monkeys, a transient but marked collapse of umbilical vasculature was observed uniformly within about 15 minutes. This <u>ethanol-induced impairment of umbilical circulation</u> produced <u>severe hypoxia</u> and <u>acidosis</u> in the fetus. Recovery occurred during the succeeding hour. This striking interruption of fetoplacental circulation may explain one of the mechanisms of <u>mental retardation</u> , a frequent manifestation in children afflicted with <u>fetal alcohol syndrome (FAS)</u> .		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00910-03 PR												
PERIOD COVERED October 1, 1981 to September 30, 1982														
TITLE OF PROJECT (80 characters or less) Role of Uteroglobin and Transglutaminase in Reproduction														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width:100%; border: none;"> <tr> <td style="width:35%;">P.I.: Anil B. Mukherjee</td> <td style="width:35%;">Chief, Section on Molecular and Developmental Genetics</td> <td style="width:30%;">PRB, NICHD</td> </tr> <tr> <td>Other: R. Manjunath</td> <td>Visiting Fellow</td> <td>PRB, NICHD</td> </tr> <tr> <td>A. Fisher</td> <td>Chemist</td> <td>PRB, NICHD</td> </tr> <tr> <td>K. Ozato</td> <td>Senior Staff Fellow</td> <td>PRB, NICHD</td> </tr> </table>			P.I.: Anil B. Mukherjee	Chief, Section on Molecular and Developmental Genetics	PRB, NICHD	Other: R. Manjunath	Visiting Fellow	PRB, NICHD	A. Fisher	Chemist	PRB, NICHD	K. Ozato	Senior Staff Fellow	PRB, NICHD
P.I.: Anil B. Mukherjee	Chief, Section on Molecular and Developmental Genetics	PRB, NICHD												
Other: R. Manjunath	Visiting Fellow	PRB, NICHD												
A. Fisher	Chemist	PRB, NICHD												
K. Ozato	Senior Staff Fellow	PRB, NICHD												
COOPERATING UNITS (if any) Elliott Schiffman, NIDR														
LAB/BRANCH Pregnancy Research Branch														
SECTION Section on Molecular and Developmental Genetics														
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205														
TOTAL MANYEARS: 1.8	PROFESSIONAL: 1.8	OTHER:												
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS														
SUMMARY OF WORK (200 words or less - underline keywords) <p>We previously reported experimental evidence that <u>uteroglobin (UG)</u> in conjunction with <u>transglutaminase (TG)</u> can mask the <u>antigenicity of implanting rabbit embryos</u> as well as <u>epididymal sperm</u>. Although the mechanism of action of uteroglobin and transglutaminase had been hypothesized no experimental data were available at that time. We have now carried out experiments with epididymal spermatozoa and <u>prostatic fluid</u> and a <u>crosslinked molecule</u> (sperm protein-UG) could be visualized in SDS-PAGE. This hybrid molecule may be the <u>cross-linked form between surface antigens and uteroglobin</u>.</p> <p>In collaboration with Dr. Schiffman and his associates we have shown that uteroglobin in micromolar concentration <u>inhibits chemotaxis of neutrophils</u> as well as <u>monocytes</u>. This may suggest yet another function of UG on the rabbit immune system and explain why the implanting embryo as well as spermatozoa do not normally elicit <u>immune response</u> in the female mammal.</p>														

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00912-03 PR												
PERIOD COVERED October 1, 1981 through September 30, 1982														
TITLE OF PROJECT (80 characters or less) Gene Regulation and Cellular Differentiation														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0" data-bbox="94 493 1157 594"> <tr> <td>P.I.:</td> <td>Janice Y. Chou</td> <td>Senior Investigator</td> <td>PRB, NICHD</td> </tr> <tr> <td>Other:</td> <td>Fumiyuki Ito</td> <td>Visiting Fellow</td> <td>" "</td> </tr> <tr> <td></td> <td>Richard Staton</td> <td>Technician</td> <td>" "</td> </tr> </table>			P.I.:	Janice Y. Chou	Senior Investigator	PRB, NICHD	Other:	Fumiyuki Ito	Visiting Fellow	" "		Richard Staton	Technician	" "
P.I.:	Janice Y. Chou	Senior Investigator	PRB, NICHD											
Other:	Fumiyuki Ito	Visiting Fellow	" "											
	Richard Staton	Technician	" "											
COOPERATING UNITS (if any) F.W. Ruscetti and R.C. Gallo, NCI L.J. Rosenthal, Georgetown University														
LAB/BRANCH Pregnancy Research Branch														
SECTION Section on Endocrinology														
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205														
TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.0	OTHER: 1.0												
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS														
SUMMARY OF WORK (200 words or less - underline keywords) Topics of current interest are: 1) control of the expression of <u>human chorionic gonadotropin (hCG)</u> , <u>pregnancy-specific β-1-glycoprotein (PSβG)</u> and <u>alkaline phosphatase in placenta</u> , <u>SV40 tsA-transformed placental, choriocarcinoma</u> , and <u>nontrophoblastic tumor cells</u> ; 2) control of the expression of <u>α-fetoprotein (AFP)</u> , <u>albumin</u> , and <u>transferrin in liver</u> , <u>SV40 tsA-transformed liver</u> , and <u>hepatoma cells</u> ; 3) <u>biosynthesis and processing of AFP</u> , <u>albumin and transferrin in liver cells</u> ; 4) <u>biosynthesis and processing of hCG</u> , <u>PSβG</u> and <u>alkaline phosphatase in placental cells</u> .														

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 HD 00913-03 PR

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Primate Models for In Vitro Fertilization and Alternatives

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	G.D. Hodgen	Chief	PRB, NICHD
Other:	O. Kreitmann	Guest Scientist	PRB, NICHD
	B. Cowan	Guest Scientist	PRB, NICHD
	R. Schenken	Guest Scientist	PRB, NICHD

COOPERATING UNITS (if any)

LAB/BRANCH

Pregnancy Research Branch

SECTION

Section on Endocrinology

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, MD 20205

TOTAL MANYEARS:

1.5

PROFESSIONAL:

1.0

OTHER:

0.5

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS

(b) HUMAN TISSUES

(c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

We have developed procedures for oocyte aspiration from the preovulatory follicle, in vitro fertilization, embryo culture and an alternative low tubal ovum transfer surgical procedure allowing in vivo fertilization. Restrospective analysis demonstrated that aspiration of the preovulatory follicle often induced corpus luteum dysfunction. Further, we have assessed cleavage rates of monkey embryos in vitro, finding that their retarded progression may be a major obstacle in successful in vitro fertilization with embryo transfer. To test for inherent versus environmental deficiencies that may impair embryonic development before implantation, we devised an egg-embryo chamber that is used in the abdomen. Passage of peritoneal fluids nurtures the embryo so that normal development can occur.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00914-03 PR
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PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Fallopian Tube Dysfunction and Endometriosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	G.D. Hodgen	Chief	PRB, NICHD
Other:	E.L. Marut	Clinical Associate	PRB, NICHD
	L.B. Werlin	Clinical Associate	PRB, NICHD
	R.S. Schenken	Guest Scientist	PRB, NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Pregnancy Research Branch

SECTION
Section on Endocrinology

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 1.1	PROFESSIONAL: 1	OTHER: 0.1
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The major cause of human infertility in the U.S.A. is tubal dysfunction. Endometriosis and other causes of failure to achieve satisfactory gamete transport are major contributing factors. We sought to examine how these infertilities arise and how to better treat them medicinally and surgically. On-going studies have compared the effectiveness of Danazol vs GnRH agonists/antagonists in reducing pelvic lesions arising from induced endometriosis.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00916-02 PR
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PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Studies of Corpus Luteum Function in the Cycling and Pregnant Monkey: Relaxin Secretion

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Wilbert E. Nixon	Senior Investigator	PRB, NICHD
Other:	Rudolph Reid	Technician	PRB, NICHD
	Bodour M. Abou-Hozalifa	Guest Worker	PRB, NICHD
	Robert Williams	Sr. Staff Fellow	PRB, NICHD
	Richard Stouffer	Univ. Arizona Med. Sch.	
	Gary D. Hodgen	Chief	PRB, NICHD

COOPERATING UNITS (if any)
Dept. of Physiology
University of Arizona Medical School

LAB/BRANCH
Pregnancy Research Branch

SECTION
Section on Endocrinology

INSTITUTE AND LOCATION
NICHD, Bethesda, MD 20205

TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.5	OTHER: 0.5
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CHECK APPROPRIATE BOX(ES)
 (a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER
 (a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)
 Secretion of relaxin by the cynomolgus monkey has been studied during the menstrual cycle and during pregnancy. That the corpus luteum was the major source of relaxin during the menstrual cycle and during pregnancy was supported by greater than 80 percent decline in levels found in ovarian venous blood within 30 minutes of luteectomy by dissection. The effect of the conceptus on relaxin secretion was assessed by fetectomy (Fx) of 3 monkeys at 80 days gestation and placentectomy (Plx) at 22 weeks (term = 24 weeks). No change in relaxin secretion was observed following Fx, but Plx resulted immediately in decreased progesterone levels while relaxin levels decreased slowly over several weeks. Simulation of early pregnancy by daily hCG administrations during the nonfertile menstrual cycle resulted in extended luteal phases characterized by decreasing progesterone and increasing and sustained relaxin secretion. A gonadotropin regimen characterized by both its strength and duration appears necessary for relaxin secretion in this primate. In vitro incubation of luteal cells from hCG stimulated ovaries secreted minimal progesterone and significant relaxin.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00917-02 PR
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) Gene Transfer by Chromosomes, Lipochromosomes and Liposome Encapsulated DNA		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
P.I.: Anil B. Mukherjee	Chief, Section on Molecular and Developmental Genetics	PRB, NICHD
Other: William Rizzo M. Rampertaap	Clinical Associate Stay-in-School	NPMB, NICHD PRB, NICHD
COOPERATING UNITS (if any) Dr. Judith Levin, Lab Molecular Genetics, NICHD		
LAB/BRANCH Pregnancy Research Branch		
SECTION Section on Molecular and Developmental Genetics		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205		
TOTAL MANYEARS: 2.5	PROFESSIONAL: 2.5	OTHER:
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) <u>Chromosome mediated gene transfer</u> is a powerful tool for studies on the organization and regulated <u>expression of genetic information</u> . The potential application of this approach to investigate <u>retrovirus system</u> has been studied. The results demonstrate that the AKR MuLV genome can be stably transferred to uninfected recipient cells via isolated metaphase chromosomes or by <u>lipochromosomes</u> . Although AKR virus are not able to infect heterologous cells, chromosome-mediated and lipochromosome mediated transfection resulted in the establishment of productive AKR-MuLV infection in mink cells. Thus, the use of chromosomes or lipochromosomes to transfer viral genes can circumvent the natural <u>host restriction barrier</u> . In other experiments SV40 viral genome has been successfully transferred to non-infected cells at a high frequency via liposome encapsulated DNA.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00918-01 PR												
PERIOD COVERED October 1, 1981 to September 30, 1982														
TITLE OF PROJECT (80 characters or less) Mechanism of Suppression of Immune Response to Paternal Transplantation Antigens by Pregnant Female														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width:100%; border: none;"> <tr> <td style="width:35%;">P.I.: Ozato, K.</td> <td style="width:35%;">Senior Staff Fellow</td> <td style="width:30%;">PRB, NICHD</td> </tr> <tr> <td>Harrington, B.</td> <td>Chemist</td> <td>PRB, NICHD</td> </tr> <tr> <td>Seidman, C.</td> <td>Summer Student</td> <td>PRB, NICHD</td> </tr> <tr> <td>Mukherjee, A.B.</td> <td>Head, Section on Molecular and Developmental Genetics</td> <td>PRB, NICHD</td> </tr> </table>			P.I.: Ozato, K.	Senior Staff Fellow	PRB, NICHD	Harrington, B.	Chemist	PRB, NICHD	Seidman, C.	Summer Student	PRB, NICHD	Mukherjee, A.B.	Head, Section on Molecular and Developmental Genetics	PRB, NICHD
P.I.: Ozato, K.	Senior Staff Fellow	PRB, NICHD												
Harrington, B.	Chemist	PRB, NICHD												
Seidman, C.	Summer Student	PRB, NICHD												
Mukherjee, A.B.	Head, Section on Molecular and Developmental Genetics	PRB, NICHD												
COOPERATING UNITS (if any) Tanaka, K., Apella, E., L.C.B., NCI														
LAB/BRANCH Pregnancy Research Branch														
SECTION Section on Molecular and Developmental Genetics														
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205														
TOTAL MANYEARS: 3.0	PROFESSIONAL: 3.0	OTHER:												
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS														
SUMMARY OF WORK (200 words or less - underline keywords) <p>In order to test the hypothesis that <u>absence of immune response</u> by the pregnant female is due to the production of <u>specific anti-idiotypic antibodies</u>, it has been necessary to develop a murine model system in which a relatively <u>dominant idiotypic</u> can be found in a given <u>anti-H2 immune response</u>. In the past year we found such a dominant idiotypic in <u>BALB/C H-2^{dm2} anti-BALB/C humoral response</u>. In addition, we have obtained several lines of evidence which point to the notion that anti-idiotypic antibodies do indeed regulate the host immune response in anti H-2 response.</p> <p>There has not been definitive proof whether and when paternal H-2 antigen is expressed in early development. In collaboration with other groups, we examined H-2 antigen expression on mouse <u>trophoblast clones</u> which maintain features of trophoblasts. We found that extremely low levels of H-2 antigen is expressed in these clones. In this study, techniques to detect H-2 <u>gene activation</u>, <u>protein synthesis</u> and <u>surface expression</u> have been developed which will be important for the forthcoming study.</p>														

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00919-01 PR						
PERIOD COVERED October 1, 1981 to September 30, 1982								
TITLE OF PROJECT (80 characters or less) Monoclonal Antibodies Which Detect Antigens of Neuro-endocrine Tissue								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width:100%; border: none;"> <tr> <td style="width:33%;">P.I.: Ozato, K.</td> <td style="width:33%;">Senior Staff Fellow</td> <td style="width:33%;">PRB, NICHD</td> </tr> <tr> <td>Other: Ben-Barack, J.</td> <td>Summer Student</td> <td>PRB, NICHD</td> </tr> </table>			P.I.: Ozato, K.	Senior Staff Fellow	PRB, NICHD	Other: Ben-Barack, J.	Summer Student	PRB, NICHD
P.I.: Ozato, K.	Senior Staff Fellow	PRB, NICHD						
Other: Ben-Barack, J.	Summer Student	PRB, NICHD						
COOPERATING UNITS (if any) H. Gainer, Chief, LDN, NICHD								
LAB/BRANCH Pregnancy Research Branch								
SECTION Section of Molecular and Developmental Genetics								
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205								
TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:						
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS								
SUMMARY OF WORK (200 words or less - underline keywords) An attempt has been made to identify and study by <u>hybridoma technology</u> a <u>library of new antigens specific for tissues with neuroendocrine function</u> such as <u>hypothalamus, pituitary, and placental tissues</u> . Mice were immunized with polymerized antigens prepared from these tissues. Hybridoma clones producing antibodies that reacted with antigens in the tissue were established on the basis of <u>ELISA and RIA</u> . Identification of each antigenic molecule can be achieved by the <u>immunoblot technique</u> . Localization of antigens in tissue has been studied by <u>immunocytochemical evaluation</u> . <u>Monoclonal antibodies specific for neurophysin</u> antigens in hypothalamus and <u>posterior pituitary</u> are expected to help dissect the <u>molecular heterogeneity</u> of neurophysins.								

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00920-01 PR																
PERIOD COVERED October 1, 1981 to September 1982																		
TITLE OF PROJECT (80 characters or less) Mouse Transplantation Antigeny (H-2) Genes: DNA Sequence Basis for Immunological Parameters Associated with H-2 Antigens																		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0"> <tr> <td>P.I.:</td> <td>K. Ozato</td> <td>PRB</td> <td>NICHD</td> </tr> <tr> <td>Other:</td> <td>D. Margulies</td> <td>LMG</td> <td>NICHD</td> </tr> <tr> <td></td> <td>G. Evans</td> <td>LMG</td> <td>NICHD</td> </tr> <tr> <td></td> <td>B. Shykind</td> <td>Summer Student</td> <td>NICHD</td> </tr> </table>			P.I.:	K. Ozato	PRB	NICHD	Other:	D. Margulies	LMG	NICHD		G. Evans	LMG	NICHD		B. Shykind	Summer Student	NICHD
P.I.:	K. Ozato	PRB	NICHD															
Other:	D. Margulies	LMG	NICHD															
	G. Evans	LMG	NICHD															
	B. Shykind	Summer Student	NICHD															
COOPERATING UNITS (if any) J. Seidman, Dept. of Genetics, Harvard Medical School																		
LAB/BRANCH Pregnancy Research Branch																		
SECTION Section on Molecular and Developmental Genetics																		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205																		
TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.5	OTHER: 0.5																
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																		
SUMMARY OF WORK (200 words or less - underline keywords) <p>In the past 3 years K. Ozato has studied the degree of unusually extensive <u>polymorphism</u> and <u>molecular heterogeneity</u> of mouse <u>H-2 antigens</u> by developing <u>monoclonal antibodies</u>. Recent <u>recombinant DNA technology</u> allowed us to isolate several H-2 like genes from BALB/c genome directly. The transfer of such isolated genes into mouse L-cells has been achieved. We detected expression of the transferred genes by testing the reactivity of monoclonal antibodies of defined specificity. The assignment by the antibodies agreed with DNA sequence results. Thus we identified 2 genes to be <u>H-2 L^d</u> and <u>D^d</u>. The new genes have been evaluated for various immunological parameters, such as ability to elicit antibody response, recognition by <u>alloreactive</u> or <u>hapten</u> (virus) specific H-2 restricted T cells. These studies provided the <u>foundation</u> for the next step for determining precise DNA sequence responsible for the immunological parameters described above.</p>																		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

201 HD 00921-01 PR

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Fetal Diagnosis and Therapeutics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Donald R. Mattison	Medical Officer	PRB, NICHD
Other:	Jeffrey C. King	Guest Scientist	PRB, NICHD
	Doris Pfeiffer	Guest Scientist	PRB, NICHD

COOPERATING UNITS (if any)

LAB/BRANCH

Pregnancy Research Branch

SECTION

Section on Endocrinology

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, MD 20205

TOTAL MANYEARS:

1.0

PROFESSIONAL:

1.0

OTHER:

0

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS

(b) HUMAN TISSUES

(c) NEITHER

(a1) MINDORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The utility of a non-human primate model for development of diagnostic and therapeutic approaches to the fetus has been explored. Monkeys appear to represent useful experimental animals for exploring modifications of fetoscopy equipment and experimental approaches for fetal diagnosis and therapy.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00922-01 PR
PERIOD COVERED October 1, 1981 through September 30, 1982		
TITLE OF PROJECT (80 characters or less) Nuclear Transfer in Mammalian Oocytes		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT P.I.: Bela J. Gulyas Senior Investigator PRB, NICHD		
COOPERATING UNITS (if any)		
LAB/BRANCH Pregnancy Research Branch		
SECTION Section on Endocrinology		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205		
TOTAL MANYEARS: 1	PROFESSIONAL: 1	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Developing methods are in progress for <u>nuclear transfer</u> in mammalian oocytes. The initial problems of simulation have been solved. A technique was also developed for fusing oocytes, which in turn are capable of continuing development to the 14 somite stage. The <u>fusion technique</u> appears promising as a means of introducing donor nucleus in future research.		

ANNUAL REPORT

DEVELOPMENTAL PHARMACOLOGY BRANCH

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

October 1, 1981 to September 30, 1982

Table of Contents

SUMMARY

PROJECT REPORTS

- Z01 HD 00032-09: Conformations and Interactions of Proteins and Nucleic Acids in Solution
- Z01 HD 00136-14: Pharmacogenetics
- Z01 HD 00137-08: Genetic Regulation of Drug-Conjugating Enzymes
- Z01 HD 00500-04: Hormonal Regulation of Gene Expression
- Z01 HD 00501-05: Non-Invasive Studies of Cell Metabolism Using Nuclear Magnetic Resonance Methods

NICHD ANNUAL REPORT
October 1, 1981 through September 30, 1982
Developmental Pharmacology Branch

SUMMARY

The DEVELOPMENTAL PHARMACOLOGY BRANCH studies the molecular mechanisms underlying genetic differences involved in the stimulation of enzymes which metabolize drugs, carcinogens, and other environmental pollutants. Why does the same dose of the same drug or other foreign compound given to two different individuals (with the exception of monozygotic twins) evoke different responses? The responses include not only therapeutic effectiveness of a drug, but also undesirable side effects such as tissue necrosis, cancer, and birth defects. Our studies are conducted with a variety of biological systems, each chosen so as to provide unique experimental access and unequivocal answers to the questions being asked: inbred strains of mice, established cell culture lines, and recombinant DNA technology. The Branch presently comprises one Section and four Units.

A. The Section on Pharmacogenetics and Molecular Teratology, under the direction of Daniel W. Nebert, M.D., studies the relationship between the etiology of birth defects and the genetic regulation of drug-metabolizing enzymes. The teratogenic, carcinogenic, or toxic effects of certain drugs and other foreign compounds may reflect important genetically mediated differences between individual laboratory animals or individual humans. Our laboratory has developed experimental model systems for studying drug metabolism in cell culture and in a colony of inbred strains of mice. We have determined that the induction of several dozen drug-metabolizing enzyme "activities" is regulated at one or two genetic loci, called the Ah locus (for aromatic hydrocarbon responsiveness). The relative "aromatic hydrocarbon responsiveness" among siblings in the uterus or as children results in genetic differences in: chemical-initiated tumors, aplastic anemia, or leukemia; paralysis times when given a certain muscle relaxant; survival times when dosed with several environmental pollutants; hepatic necrosis and cataract formation when given acetaminophen; number of fetal resorptions, stillbirths, and malformations when the pregnant mother is given certain chemicals; and ovarian toxicity and infertility. There is ample evidence for the Ah locus in the human. Because of these genetically mediated dissimilarities in foreign chemical metabolism, we have suggested it is possible to explain in the human why "drug-induced syndromes" occur in one child although the mother has received the same dose of the same drug for two or more pregnancies. We have developed an assay for the Ah receptor, which appears to be the major regulatory gene product for this complex. We also have several P-450 cDNA clones with which P-450 mRNA levels can be accurately measured. An excellent correlation exists between the intranuclear appearance of the inducer-receptor complex and synthesis of new P1-450 mRNA.

B. The Unit on Molecular Genetics, under the direction of Masahiko Negishi, Ph.D., has developed antibodies to several of the structural gene products (membrane-bound forms of cytochrome P-450) for use as probes to understand further the genetic regulation of drug-metabolizing enzymes. With the aid of these antibodies, we have been able to "size" mRNA associated with several P-450 proteins, through the use of translation in vitro. Knowing the size, we have enriched for this mRNA and have isolated and characterized more

than six cDNA clones of different P-450 structural genes. We also have cloned the mouse genomic P1-450 gene from rat, rabbit, and human. With these cloned genes, we should know soon the answers to such questions as genetic linkage, mechanisms of regulation of P-450 induction, and evolutionary phylogeny of this enzyme system (which exists in certain bacteria and apparently all eukaryotes). With these clones, we also hope to develop sensitive assays for predicting individual humans at increased risk for certain birth defects, other drug toxicities, or cancers.

C. The Unit on Genetic Expression, under the direction of Howard J. Eisen, M.D., studies the mechanism of action of glucocorticoid hormones. The glucocorticoid receptor is purified by DNA-cellulose chromatography, and anti-receptor antibodies are prepared for use in determining the chemical structure and biochemical function of the receptor. Antibodies directed against human glucocorticoid receptors have been produced and are being used to investigate the genetics of human glucocorticoid receptors and the mechanisms of glucocorticoid resistance in human diseases. We have used immunochemical methods and affinity labeling to isolate ³H-labeled glucocorticoid receptors from rodent and human cells. These studies provide the first covalently labeled receptor preparations suitable for detailed chemical analysis of the glucocorticoid receptor.

D. The Unit on Genetic Regulation of Drug-conjugating Enzymes, under the direction of Ida S. Owens, Ph.D., is interested in the genetic regulation of basal and inducible UDP glucuronosyltransferase enzymes among inbred mouse strains and cell culture. Detoxication of highly lipophilic endogenous substrates--such as bilirubin and steroids--therapeutic medications, and environmental pollutants requires a multistep process involving oxidative metabolism (phase I reactions) and conjugation to glucuronic acid of oxidized product (phase II reactions) to hasten excretion of these endogenous and foreign intermediates. In order to study the heterogeneity, regulation, and ultimately the molecular properties of UDP glucuronosyltransferases, we have used protein-charge heterogeneity that allows one to purify particular forms of enzyme. Using column isoelectric-focusing, we have described isoelectric points for various forms of transferases with 21 different substrates; the results indicate that there are three classes of substrates. One group of substrates (represented by estrone and phenolphthalein) is conjugated by enzymes with high pI values (8.5), a second group (represented by 1-naphthol and 4-hydroxybiphenyl) is conjugated by enzymes with low pI values (6.7); a third group of substrates (4-methylumbelliferone and p-nitrophenol) is conjugated equally by high and low pI enzymes. 3-Methylcholanthrene induces primarily high pI forms, whereas phenobarbital induces both high and low pI forms. The clinically significant bilirubin UDP glucuronosyltransferases have a pI value of ~7.5 (studies are being extended to attempt to identify other bilirubin transferases which are suggested by genetic studies). We adjusted ion exchange and affinity chromatography such that a low pI transferase was highly purified. An apparently "monospecific" antibody was developed. Immunoprecipitation studies indicate that many low pI activities may have a common antigenic site or one enzyme. Isoelectric-focusing studies suggest that multiple forms exist in the low pI fractions to account for the activities. With the aid of the antibody, transferase-specific mRNA was translated into a protein with the molecular weight identical to the purified transferase. We now plan to enrich for this mRNA by antibody precipitation of transferase-specific polysomes. The enriched mRNA will be further

characterized with respect to size and reverse-transcribed into a cloned cDNA probe. The successful cloning of a transferase gene should then allow one to isolate the appropriate genomic clone in order to study the genetic expression of numerous transferases.

E. The Unit on Physical Biology, under the direction of Jack S. Cohen, Ph.D., examines the structure and interactions of biological molecules in detail in solution and in cells using several nuclear magnetic resonance techniques. Observations of doublet resonances in ^{31}P NMR spectra of sonicated double-stranded polydeoxynucleotides lead to the conclusion that they can exhibit secondary structure effects in their backbone conformations, depending on the base sequence and the solution conditions. Extensive studies of four different sequences in five salts at different concentrations and temperatures show that; (a) poly(dA).poly(dT), which exists as a regular right-handed B-form, shows no transitions; (b) poly(dAdT).poly(dAdT) goes from an alternating B-form in low salt to an alternating C-type form in high salt, but to a uniform A-form in ethanol; (c) poly(dGdC).poly(dGdC) goes from a regular B-form in low salt to an alternating (left-handed) Z-form in very high salt; (d) poly(dGm⁵dC).poly(dGm⁵dC) exists as an alternating B-form in very low salt and is transformed to an alternating Z-form in high salt, but at concentrations very much lower than the unmethylated analog. It should be noted that the sequence (m⁵CG) occurs in eucaryotic DNA, and consequently the distinctions between the secondary structure changes of these DNA's may well have genetic significance. To extend these studies to the deoxyribose ring we have obtained ^{13}C NMR spectra at natural abundance (1.1% ^{13}C). Due to the low sensitivity and low enrichment of this nucleus, the new NT500 NMR spectrometer has been used and it has been found that the C2' and C3' signals of poly(dAdT).poly(dAdT) are completely resolved into doublets at 125 MHz, presumably corresponding to the C2'-endo and C3'-endo conformations of the sugar backbone. In current work these ^{13}C NMR studies are being extended to other sequences. ^{31}P and ^1H NMR are also being applied to study metabolism in cells noninvasively. Thus far, four cancer cell lines grown in culture have been subjected to preliminary analysis. One problem associated with these studies is that the cells are usually employed as a dense suspension (ca 10^8 cells) in the NMR tube. To avoid rapid decay of the sample and to have controlled conditions, a perfusion system has been developed in which the cells are maintained in a chamber while spectra are collected. It is also desirable to apply ^{13}C NMR to study the metabolism of ^{13}C -enriched metabolites or drugs. Because of the low sensitivity of this nucleus, experiments are underway to observe ^{13}C NMR spectra, but at the sensitivity of ^1H NMR; this could greatly extend the range of selective metabolic studies by the NMR methods. Also, the internal pH of cells can be determined by the NMR method. Previous ^{31}P NMR observations showed an anomalous titration of ATP in chromaffin granules; currently ^1H NMR experiments are underway to explain this phenomenon. We are comparing these results with those from other secretory granules.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00032-09 DP		
PERIOD COVERED October 1, 1981 to September 30, 1982				
TITLE OF PROJECT (80 characters or less) Conformations and Interactions of Proteins and Nucleic Acids in Solution				
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT				
PI:	Jack S. Cohen	Research Chemist	DP	NICHD
OTHER:	Chi-Wan Chen Lou J. Hughes C.-H. Niu Michael Behe Richard Knop	Staff Fellow IPA Guest Staff Fellow Staff Fellow Clinical Associate	DP DP LBP LMB MOB	NICHD NICHD NIADDK NIADDK NCI
COOPERATING UNITS (if any) Laboratory of Chemical Physics, NIADDK (for spectrometer maintenance)				
LAB/BRANCH Developmental Pharmacology Branch				
SECTION Unit on Physical Biology				
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205				
TOTAL MANYEARS: 27/12		PROFESSIONAL: 27/12		OTHER:
CHECK APPROPRIATE BOX(ES)				
<input type="checkbox"/> (a) HUMAN SUBJECTS				
<input type="checkbox"/> (b) HUMAN TISSUES				
<input checked="" type="checkbox"/> (c) NEITHER				
<input type="checkbox"/> (a1) MINORS				
<input type="checkbox"/> (a2) INTERVIEWS				
SUMMARY OF WORK (200 words or less - underline keywords)				
<p>To elucidate the <u>conformation</u> and interactions of <u>nucleic acids</u> and <u>proteins</u> in solution by <u>nuclear magnetic resonance</u> (NMR) methods. Particularly to investigate the interactions of <u>DNA</u> with proteins and drugs, alone and in nucleoprotein complexes.</p>				

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00136-14 DP
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) PHARMACOGENETICS		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: D.W. Nebert - Chief, DPB & Head, Section on Pharmacogenetics and Molecular Teratology - NICHD OTHER: SEE ATTACHMENT I		
COOPERATING UNITS (if any) SEE ATTACHMENT II		
LAB/BRANCH Developmental Pharmacology Branch		
SECTION Section on Pharmacogenetics and Molecular Teratology		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 133/12	PROFESSIONAL: 112/12	OTHER: 21/12
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) In certain instances, <u>human pharmacogenetic disorders</u> cause individuals to react very differently to the same dose of the same drug. The <u>teratogenic, carcinogenic, or toxic effects</u> of certain <u>drugs</u> and other foreign compounds also may reflect important genetically mediated differences among individuals. Accordingly, our laboratory has developed experimental model systems for studying drug metabolism with <u>recombinant DNA technology</u> , in <u>cell culture</u> , and among <u>inbred strains of mice</u> . The <u>Ah locus</u> regulates the induction of a small subset of all the <u>multiple cytochromes P-450</u> . The <u>Ah receptor(s)</u> controls this induction process. We have isolated and characterized the <u>genomic P1-450 gene</u> and <u>cDNA clones</u> for P2-450 and P _T -450. The mouse P1-450 clone cross-hybridizes to the corresponding gene from rat, rabbit and human. With such clones we hope to understand the mechanisms of P-450 induction by drugs, to gain insight into the evolution of P-450 (present in plasmids and all eukaryotes), and to develop sensitive tests to determine clinically who is at increased risk for various drug-induced <u>birth defects</u> , other forms of <u>drug toxicity</u> , and <u>environmentally-caused malignancies</u> . 382		

ATTACHMENT I

M. Altieri	Visiting Fellow	DP	NICHD
S.W. Bigelow	Chemist	DP	NICHD
Y.-T. Chen	Visiting Associate	DP	NICHD
W.P. Hausdorff	Biologist	DP	NICHD
L.M. Hjelmeland	Senior Staff Fellow	DP	NICHD
T. Ikeda	Guest Worker	DP	NICHD
D.J. Kessler	Chemist	DP	NICHD
R.A. Lazarte	Visiting Scientist	DP	NICHD
R.C. Levitt	Clinical Associate	DP	NICHD
M. Negishi	Visiting Scientist	DP	NICHD
T. Ohyama	Visiting Fellow	DP	NICHD
I. Stupans	Visiting Fellow	DP	NICHD
R.H. Tukey	Staff Fellow	DP	NICHD

ATTACHMENT II - COOPERATING UNITS:

- L. S. Andrews, Dept. of Food Animal Additives Evaluation Branch, Federal Building #8, 200 C Street, S.W., Washington, D.C.
- E. A. Bababunmi, Dept. of Biochemistry, University of Ibadan, Ibadan, Nigeria.
- A. C. Collins, Institute for Behavioral Genetics, University of Colorado, Boulder, Colorado 80309
- H. J. Eisen, Unit on Genetic Expression, Developmental Pharmacology Branch, NICHD, NIH, Bethesda, Maryland 20205
- J. E. Gielen, University of Liege, Belgium
- T. J. Gill, III, Dept. of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania 15261
- O. Hankinson, Dept. of Molecular Biology, Stanley Hall, University of California, Berkeley, California 94720
- M. E. Harper, Agouron Institute, La Jolla, California 92037
- D. E. Harrison, The Jackson Laboratory, Bar Harbor, Maine 04609
- R. E. Kouri, Dept. of Biochemical Oncology, Microbiological Associates, 5221 River Road, Bethesda, Maryland 20016
- C. Kozak, Laboratory of Viral Diseases, NIAID, NIH, Bethesda, Maryland 20205
- P. Lalley, Oak Ridge National Laboratory, Box Y, Oak Ridge, Tennessee 37830
- I. P. Lee, Laboratory of Reproductive and Development Toxicology, NIEHS, Research Triangle Park, North Carolina 27709
- A. S. Levine, Pediatric Oncology Branch, NCI, NIH, Bethesda, Maryland 20205
- A. M. Malkinson, School of Pharmacy, University of Colorado, Boulder, Colorado 80309
- D. R. Mattison, Pregnancy Research Branch, NICHD, NIH, Bethesda, Maryland 20205
- A. B. Okey, Dept. of Paediatrics, Division of Clinical Pharmacology, The Hospital for Sick Children, Toronto, Ontario, Canada
- J. C. Osborne, Laboratory of Biochemical Genetics, Molecular Disease Branch, NHLBI, NIH, Bethesda, Maryland 20205
- I. S. Owens, Unit on Drug-Conjugating Enzymology, Developmental Pharmacology Branch, NICHD, NIH, Bethesda, Maryland 20205
- O. Pelkonen, Dept. of Pharmacology, University of Oulu, Oulu, Finland

F. Ruscetti, Building C-327, 5516 Nicholson Lane, Litton Bionetics,
Kensington, Maryland 20795

J. E. Womack, Dept. of Veterinary Pathology, Texas A & M University, College
Station, Texas 77843

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00137-08 DP										
PERIOD COVERED October 1, 1981 to September 30, 1982												
TITLE OF PROJECT (80 characters or less) GENETIC REGULATION OF DRUG-CONJUGATING ENZYMES												
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0" data-bbox="66 504 1371 604"> <tr> <td>PI:</td> <td>I. S. Owens</td> <td>Research Biologist</td> <td>DP</td> <td>NICHD</td> </tr> <tr> <td>OTHER:</td> <td>P. Mackenzie</td> <td>Visiting Fellow</td> <td>DP</td> <td>NICHD</td> </tr> </table>			PI:	I. S. Owens	Research Biologist	DP	NICHD	OTHER:	P. Mackenzie	Visiting Fellow	DP	NICHD
PI:	I. S. Owens	Research Biologist	DP	NICHD								
OTHER:	P. Mackenzie	Visiting Fellow	DP	NICHD								
COOPERATING UNITS (if any) D. W. Nebert and coworkers, Section on Pharmacogenetics & Molecular Teratology, DPB, NIH, NICHD R. Chowdbury, Albert Einstein Medical School, Bronx, New York												
LAB/BRANCH Developmental Pharmacology Branch												
SECTION Unit on Drug-Conjugating Enzymology												
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205												
TOTAL MANYEARS: 24/12	PROFESSIONAL: 24/12	OTHER: 0/12										
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS												
SUMMARY OF WORK (200 words or less - underline keywords) <p><u>Detoxification</u> studies using noxious lipophilic foreign and endogenous compounds have continued with <u>conjugation</u> reactions by <u>genetically regulated</u> (at the <u>Ah</u> locus) and phenobarbital <u>inducible</u> <u>UDP glucuronosyltransferase</u> activities. Different transferase activities using 21 substrates have been characterized for <u>charge heterogeneity</u> using a chromatofocusing system. It was shown that transferase enzymes generally have either a <u>high (~pI 8.5)</u> and/or a <u>low (~p 6.7) isoelectric point</u> such that 19 of 21 <u>substrate</u> activities varied independently after <u>inducers</u> treatment. <u>3-Methylchol-anthrene</u> induced primarily high pI form(s), while phenobarbital induced both high and low pI forms. Activities for the 12 benzo[a]pyrene phenols also segregated into these two categories. <u>Antibodies</u> against a <u>purified low pI form</u> recognize only this form and not a high pI form. These results suggest many different forms of transferase.</p>												

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00500-04 DP
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) Hormonal Regulation of Gene Expression		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Howard J. Eisen Medical Officer DP NICHD		
COOPERATING UNITS (if any) Alan Munck - Dartmouth University, Hanover, New Hampshire S. Stoney Simons, Jr. - Lab. of Chemistry, NIAMDD, NIH, Bethesda, MD.		
LAB/BRANCH Developmental Pharmacology Branch		
SECTION Unit on Hormonal Regulation of Gene Expression		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 6/12	PROFESSIONAL: 6/12	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) This project is concerned with biochemical and molecular aspects of <u>hormone action during fetal development</u> . <u>Adrenal corticosteroids</u> affect many aspects of <u>fetal development</u> and also have <u>teratogenic</u> effects in genetically-susceptible <u>inbred mouse strains</u> . The <u>glucocorticoid receptor</u> is purified by <u>DNA-affinity chromatography</u> and <u>antibodies</u> to the receptor are prepared for use in determining the chemical structure and function of the receptor.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00501-05 DP																																													
PERIOD COVERED October 1, 1981 to September 30, 1982																																															
TITLE OF PROJECT (80 characters or less) Non-Invasive Studies of Cell Metabolism Using Nuclear Magnetic Resonance Methods																																															
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0" style="width: 100%;"> <tr> <td style="width: 10%;">PI:</td> <td style="width: 40%;">Jack S. Cohen</td> <td style="width: 30%;">Research Chemist</td> <td style="width: 10%;">DP</td> <td style="width: 10%;">NICHD</td> </tr> <tr> <td>OTHER:</td> <td>David Foxall</td> <td>Visiting Fellow</td> <td>DP</td> <td>NICHD</td> </tr> <tr> <td></td> <td>Harvey Pollard</td> <td>Chief</td> <td>LEP</td> <td>NIADDK</td> </tr> <tr> <td></td> <td>Howard Burrows</td> <td>Guest Worker</td> <td>LBG</td> <td>NHLBI</td> </tr> <tr> <td></td> <td>Desmond Carney</td> <td>Staff</td> <td>MOB</td> <td>NCI</td> </tr> <tr> <td></td> <td>James Mitchell</td> <td>Cancer Expert</td> <td>ROB</td> <td>NCI</td> </tr> <tr> <td></td> <td>Richard Knop</td> <td>Clinical Associate</td> <td>MOB</td> <td>NCI</td> </tr> <tr> <td></td> <td>Gil Navon</td> <td>Visiting Scientist</td> <td colspan="2">Tel Aviv University, Israel</td> </tr> <tr> <td></td> <td>James Russel</td> <td>Staff Fellow</td> <td>LBG</td> <td>NHLBI</td> </tr> </table>			PI:	Jack S. Cohen	Research Chemist	DP	NICHD	OTHER:	David Foxall	Visiting Fellow	DP	NICHD		Harvey Pollard	Chief	LEP	NIADDK		Howard Burrows	Guest Worker	LBG	NHLBI		Desmond Carney	Staff	MOB	NCI		James Mitchell	Cancer Expert	ROB	NCI		Richard Knop	Clinical Associate	MOB	NCI		Gil Navon	Visiting Scientist	Tel Aviv University, Israel			James Russel	Staff Fellow	LBG	NHLBI
PI:	Jack S. Cohen	Research Chemist	DP	NICHD																																											
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COOPERATING UNITS (if any) SEE ATTACHED																																															
LAB/BRANCH Developmental Pharmacology Branch																																															
SECTION Unit on Physical Biology																																															
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205																																															
TOTAL MANYEARS: 32/12	PROFESSIONAL: 32/12	OTHER:																																													
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																																															
SUMMARY OF WORK (200 words or less - underline keywords) <p>NMR techniques enable signals from metabolites in tissues, cells or granules to be monitored non-invasively. ³¹P NMR is used to measure levels of <u>ATP</u>, <u>ADP</u>, <u>Pi</u>, and <u>intracellular pH</u>. NMR studies of ¹³C enriched metabolites allow the elucidation of details of their <u>metabolism</u>. Spin echo ¹H NMR enables the signals from many metabolites to be observed by removing the background of protein, membrane and water signals. These techniques are being developed and applied to several cancer cell lines grown in culture, and to several kinds of cellular secretory granules.</p>																																															

COOPERATING UNITS:

Laboratory of Chemical Physics, NIADDK (for spectrometer maintenance)
Laboratory of Experimental Pathology, NIADDK
Laboratory of Biochemical Genetics, NHLBI
Radiation Oncology Branch, NCI
Medical Oncology Branch, NCI

ANNUAL REPORT
NEONATAL AND PEDIATRIC MEDICINE BRANCH
NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

October 1, 1981 through September 30, 1982

TABLE OF CONTENTS

SUMMARY

PROJECT REPORTS

Z01 HD 00126-08 NPMB
Developmental Biology

Z01 HD 00131-08 NPMB
Human Biochemical Genetics

Z01 HD 00133-05 NPMB
Study of Glycogen Storage Disease

Z01 HD 00134-05 NPMB
Study of Prader Willi Syndrome

Z01 HD 00135-05 NPMB
Pediatric Endocrinology

Z01 HD 00402-04 NPMB
Mass Spectrometry Facility

Z01 HD 00403-01 NPMB
Magnesium Metabolism in Mothers and Neonates

NICHD ANNUAL REPORT

NEONATAL AND PEDIATRIC MEDICINE BRANCH

October 1, 1981 through September 30, 1982

The Neonatal and Pediatric Medicine Branch has continued its broad base of research focused on the problem of clinical diseases of children and the understanding of their mechanisms. The areas included are pediatric endocrinology, clinical genetics, nutrition and the study of fetal lung metabolism.

In the past year, Dr. Norman Kretchmer's lab on Developmental Gastroenterology has been closed due to the departure of the Principal Investigator, as have those studies relating to hypoglycemia led by Dr. Marvin Cornblath who has departed. A new Branch Chief, Dr. Michael Zasloff, was appointed at the end of the year. His areas of expertise and interests are clinical genetics and the basic genetic mechanisms. As of this date he has not had a chance to initiate his clinical studies in the Branch.

I. Section on Developmental Biology and Clinical Nutrition

a) The studies of developmental hormonal mechanisms controlling phospholipid biosynthesis in fetal and adult lungs continue. The studies have been broadened to include the effect of drugs such as Theophylline which appeared to be beneficial in neonatal apnea and other conditions on the lung biochemistry.

b) The studies of the Prader Willi syndrome and exogenous obesity continue.

c) The study of glycogen storage disease and the improvement of dietary management continues.

d) The Endocrine Unit is studying the mechanism of normal and abnormal sexual development in the primate. Other areas include the role of LH-RH in the development of the hypothalamic-pituitary-gonadal axis.

e) A study is under way in an attempt to define the role of magnesium in the lung and CNS development in newborn rats. Also being tested is the suspicion that dolomite, a natural magnesium source, may actually be harmful in that it has significant contaminants of iron, aluminum, chromium, lead, nickel arsenic, mercury, silicone, zinc and cadmium. Dolomite is being sold to consumers as a natural food.

II. Section on Human Biochemical and Developmental Genetics

This Section has made significant progress in the definition of the primary defect in cystinosis. They have shown that there is a specific efflux defect in the lysosomes of patients with cystinosis and that their parents show partial defects.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00126-08 NPMB
PERIOD COVERED October 1, 1981 - September 30, 1982		
TITLE OF PROJECT (80 characters or less) Developmental Biology		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT Principal Investigator: R.E. Ulane, Ph.D., Chemist, DBCN NPMB, NICHD Other Investigators: J. Graeber, M.D. C.A., DBCN NPMB, NICHD		
COOPERATING UNITS (if any) S. Compton, Dept. Physiology, Georgetown University; J. Roth, M.D., Chief, DB, NIADDK		
LAB/BRANCH Neonatal and Pediatric Medicine Branch		
SECTION Developmental Biology and Clinical Nutrition		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 2	PROFESSIONAL: 2	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The control of fetal lung development was studied by examining the number and properties of specific insulin receptors in freshly isolated fetal rat lung, lung organ culture, and primary type II pneumocyte culture. Insulin receptors are down-regulated by 50% in fetal lungs of streptozotocin-induced diabetic pregnancies. Insulin receptors in fetal lung organ culture were also shown to be down-regulated in the presence of insulin. This down-regulation was demonstrated to be coupled to a biological effect of insulin, hexose transport. Insulin receptors in organ culture could be up-regulated by removal of insulin or by the addition of hydrocortisone. Primary type II pneumocytes were shown to possess specific receptors for insulin, while lung fibroblasts exhibited very little capacity for insulin binding.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00131-08 NPMB
PERIOD COVERED October 1, 1981 - September 30, 1982		
TITLE OF PROJECT (80 characters or less) Human Biochemical Genetics		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT Principal Investigator: J. D. Schulman Head, Section HBDG, NPMB, NICHD Other Investigators: N. Bashan E.J. Butler M. Evans W. Gahl W. Rizzo D. Towne		
COOPERATING UNITS (if any) SEE ATTACHED SHEET		
LAB/BRANCH Neonatal and Pediatric Medicine Branch		
SECTION Human Biochemical and Developmental Genetics		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 11	PROFESSIONAL: 10	OTHER: 1.0
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Our studies have concerned <u>cystinosis</u> , the metabolic errors of <u>glutathione synthesis</u> and <u>degradation</u> (<u>glutathionuria</u> , <u>glutathione synthase deficiency</u> and <u>gamma glutamyl-cysteine synthase deficiency</u>), <u>glucose-6-phosphate dehydrogenase deficiency</u> in which the capacity for glutathione reduction is decreased, <u>homocystinuria</u> , <u>phenylketonuria</u> , <u>non-ketotic hyperglycinemia</u> , <u>galactosemia</u> and <u>adrenal leukodystrophy</u> . We have been interested in the development of newer forms of treatment and diagnosis for a number of these metabolic disorders and in understanding the mechanisms of disease production and related normal processes. A number of specific treatments are under investigation. Animal models of human genetic diseases are studied. Investigations have also been undertaken to explore the possibility of transferring genetic material into cells with the use of lipochromosomes. The most important advances in the past year include discovery of the etiology of cystinosis and identification of the first transmembrane lysosomal transport system for amino acids.		

COOPERATING UNITS:

L. Boxer, University of Indiana
J. Oliver, University of Connecticut
R. Berlin, University of Connecticut
P. Donahoe, Harvard
S.H. Mudd, NIMH
F. Tietze, NIAMDD
S. Kaufman, NIMH
G. Kapatos, NIMH
C. Bartsocas, University of Athens, Greece
L. Corash, University of California-San Francisco
A. Eidelman, Jerusalem, Israel
J. Robbins, NIAMDD
J. Barranger, NINDS
J. Avigan, NHLBI
H. Moser, Johns Hopkins University
D. Mattison, NICHD
M. Sheetz, University of Connecticut
S. Moses, Beersheva, Israel
N. Bashan, Beersheva, Israel
B. White, NIAMDD
J.L. Simpson, Northwestern
A. Mukherjee, NICHDS.
I. Goodman, University of Colorado
J. Schlesselman, NICHD
G. Reed, NICHD
J.A. Schneider, UCSD
J. Thoene, University of Michigan
R. Knazak, NCI

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00133-05 NPMB
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PERIOD COVERED
October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)
Study of Glycogen Storage Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator: J. B. Sidbury, M.D. Scientific Director NPMB, NICHD

Other Investigators: Y. T. Chen, M.D. Visiting Associate NPMB, NICHD

Technician: Anthony Adams NPMB, NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Neonatal and Pediatric Medicine Branch

SECTION
Developmental Biology and Clinical Nutrition

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2.50	PROFESSIONAL: 2	OTHER: .50
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Current therapy for those individuals with glycogen storage disease associated with low blood glucose is to give frequent high carbohydrate feedings during the day and a constant nocturnal nasogastric drip of glucose. This has effected a significant improvement in the care of these children. We have been working with the every 6 hour administration of corn starch as a substitute for the above regimen and find that we get improved control of the aberrant metabolic status. We are testing corn starch, potato starch and rice starch. Similar loads are given obese patients as controls.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00134-05 NPMB
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PERIOD COVERED October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)
Study of Prader Willi Syndrome

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator: J. B. Sidbury, M.D. Scientific Director NPMB, NICHD

Other Investigators: Lawrence Tamarkin, Ph.D. Staff Fellow NPMB, NICHD
Ann McNemar, RN Clinical Nurse NPMB, NICHD

Technician: Anthony Adams NPMB, NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Neonatal and Pediatric Medicine Branch

SECTION
Developmental Biology and Clinical Nutrition

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: <u>2.50</u>	PROFESSIONAL: <u>2.0</u>	OTHER: <u>.50</u>
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Circadian patterns of several hormones are determined in Prader Willi Syndrome patients and normal obese control children. The children are put on a strict weight reduction program and the circadian patterns are repeated every 6 months as long as the children lose weight. The purpose is to determine whether a consistent trend of change in pattern is seen in the obese state when the patterns are compared in the same child at normal weight.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 HD 00135-05 NPMB

PERIOD COVERED

October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)

Pediatric Endocrinology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator: Barry B. Bercu, M.D. NPMB, NICHD

Other Investigators: Byung C. Lee, M.D., Visiting Fellow NPMB, NICHD
Jose Pineda, M.D., Medical Staff Fellow NPMB, NICHD
Bessie Spiliotis, M.D. Medical Staff Fellow NPMB, NICHD

Technician: Teri Brown

Students: Robert Moy (Stay-in-school)
Stephen Plotnick (volunteer)

COOPERATING UNITS (if any)

SEE ATTACHED SHEET

LAB/BRANCH

Neonatal and Pediatric Medicine Branch

SECTION

Developmental Biology and Clinical Nutrition

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:

5.25

PROFESSIONAL:

4.0

OTHER:

1.25

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The investigations underway in our laboratory fall into a few general categories. Our primary research focus is male sexual development and, specifically, the mechanisms for the control of the onset of puberty. In our current work, we have developed a primate model, based in part on our previous rat studies. Our recent significant findings include: decreased inhibition of GnRH during puberty; "pubertal brain maturation" advancement in absence of gonadal feedback; occasional large gonadotropin pulses in prepubertal animals; pubertal development association with changes in amplitude not frequency of gonadotropin pulses; increased LH bioassay/LH radioimmunoassay ratio during puberty in castrated male; age-related changes in FSH sensitivity in primate Sertoli cell.

We have also used the primate model in our studies on neuroendocrine control of GH secretion. We have extended our clinical studies and demonstrated significant alterations in GH pulsatile secretory patterns in patients with leukemia and GH deficiency. In another clinical observation we have shown significantly increased growth in GH deficient children treated with bio-synthetic hGH.

398

COOPERATING UNITS:

W. Bardin, Rockefeller University

J. Rivier, Salk Institute

G. August, and W. Hung, Children's Hospital National Medical Center and
George Washington University

J. Shapiro, Clinical Center, NIH

G. Hodgen, PRB, NICHD

H. Hoffman, EBRP, NICHD

G. Bialy and M. Karten, CPRB, NICHD

D. Poplack, NCI

W. Mendelsonhn, NIMH

W. Sonis, CFRB, NICHD

D. Gregor, University of Maryland

PERIOD COVERED

October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)

Mass Spectrometry Facility

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Principal Investigator: Alfred L. Yergey, Ph.D. Research Chemist NPMB, NICHD

Other Investigators: Lawrence Tamarkin, Ph.D. Staff Fellow NPMB, NICHD
Nancy Vieira Biologist NPMB, NICHD

COOPERATING UNITS (if any) R. Cotter, Johns Hopkins; Peter Klein, Baylor College of Medicine; N. Gershfeld, LPB, NIAMDD; M. Friedman, U.S. Army; J.B. Sidbury, NPMB, NICHD; John Daly, NIADDK; M. Lippman, DCT, NCI; B. Chabner, DCT, NCI; B. Goldman, Worcester Fnd, Exp. Biol., MA; T. Wehr, LSC, NIMH; K. Catt, ERB, NICHD.

LAB/BRANCH

OSD, Neonatal and Pediatric Medicine Branch

SECTION

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:

4.0

PROFESSIONAL:

4.0

OTHER:

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Quantitative analysis using solids inlet probe is being done for studies of human calcium metabolism in lactation and metabolic disorders. Thermal desorption mass spectrometry of involatile organic salts has been developed for detection and identification. Mathematical modeling of calcium kinetics and quadru-pole mass filters is being done. Multivariate statistical methods are being applied to large mass spectral data sets.

The physiologic role and regulation of the pineal hormone melatonin is being studied in human subjects and animals. Plasma melatonin is being studied in obese children, in precociously pubescent children, and in women with breast cancer. Pineal melatonin is being measured in rodents to investigate the circadian regulation of this hormonal and its ontogeny. Estrogen and progesterone receptors are being measured in hamster uteri to study the effect of acute melatonin treatment on these receptors. The inhibitory effect of melatonin on the induction of mammary tumors in dimethylbenzathracene treated rats is being studied. In-vitro production of melatonin by a single chicken pineal gland is being studied.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00403-01 NPMB
PERIOD COVERED		
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;">MAGNESIUM METABOLISM IN MOTHERS AND NEONATES</p>		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT Principal investigator: Joan L. Caddell, M.D., Guest worker, NPMB, NICHD Other investigators: Joan Blanchette-Mackie, Ph. D., Senior Scientist, NIADK Anthony J. Adams, Biologist, NPMB, NICHD		
COOPERATING UNITS (if any)		
LAB/BRANCH Neonatal and Pediatric Medicine Branch		
SECTION Developmental Biology and Clinical Nutrition		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 1	PROFESSIONAL: .50	OTHER: .50
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER except for review of records at this time. <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The <u>magnesium deficiency syndrome</u> is most severe in the youngest mammals; they may develop <u>apnea</u> and <u>bradycardia</u> . We are reviewing records of <u>St. Louis neonates</u> with these findings; some infants were diagnosed as magnesium deficient and treated with magnesium. We will explore the feasibility of conducting a properly controlled study in neonates. We are exploring the <u>congenital magnesium deficiency syndrome</u> , studying the concentration of magnesium and other cations in tissues of young <u>rat pups</u> born to <u>dams</u> fed 5 to 150 mg of magnesium/ 100 g purified diet. The <u>kidney</u> of the magnesium deficient mammal avidly retains magnesium. We are studying the effect of parenteral <u>furosemide</u> in weanling and young adult rats fed several levels of dietary magnesium. The physical state and the renal excretion and tissue levels of several cations will be examined. Although weanling rats suffered no ill effect, rat dams fed 150 mg of magnesium as laboratory grade MgCO ₃ suffered high fetal wastage. We will compare this with a) dams fed certified MgCO ₃ and b) dams fed <u>dolomite</u> , which is CaMg(CO ₃) ₂ , marketed in an unrefined state for human consumption. We are studying <u>cardiopulmonary histopathology</u> in acute Mg deficiency.		

1982 ANNUAL REPORT

Endocrinology and Reproduction Research Branch

<u>Project Numbers</u>	<u>Project Title</u>	<u>Principal Investigator</u>
Z01 HD 00022-09	Renin-Angiotensin System and Aldosterone Regulation.....	G. Aguilera
Z01 HD 00035-10	The Structure and Function of Biologically Active Molecules	J. Morell
Z01 HD 00040-07	Experimental and Theoretical Studies of Hormone Receptor Interaction and Response Coupling	D. Rodbard
Z01 HD 00041-07	Cardiovascular Effects of Thyroid, Hormones, Catecholamines and Cardiotoxic Drugs	D. Rodbard
Z01 HD 00043-07	Mathematics and Statistics of Radioligand Assays	D. Rodbard
Z01 HD 00146-07	Structure and Function of Chorionic Gonadotropins	H. Chen
Z01 HD 00147-07	Mechanism of Action of Peptide Hormones in Steroidogenic Cells.....	M. Dufau
Z01 HD 00148-07	Ontogeny of Gonadotropin Receptors and Gonadal Function	K. Catt
Z01 HD 00149-07	Bioassay of Serum Luteinizing Hormone (LH) and Chorionic Gonadotropin	M. Dufau
Z01 HD 00150-07	Characterization and Purification of LH/hCG Receptors and Adenylate Cyclase	M. Dufau
Z01 HD 00151-07	Receptor-Mediated Regulation of Gonadal Function	K. Catt
Z01 HD 00160-07	Biology of the Adrenocortical Cell: Molecular Events in Steroid Biosynthesis and Secretion	C. Strott
Z01 HD 00165-07	Isolation and Characterization of Protein Hormones & Other Active Proteins	A. Chrambach
Z01 HD 00171-06	Other PAGE Instrumentation and Procedures	A. Chrambach
Z01 HD 00174-06	Hormonal Control of Ovarian Proteoglycan Synthesis	D. Rodbard
Z01 HD 00184-04	Regulation of Pituitary Hormone Secretion	K. Catt
Z01 HD 00185-03	Effect of Temperature and Other Physical Factors on Localization, Natural History and Susceptibility to Disease	D. Rodbard
Z01 HD 00187-03	Hormonal Regulation of Cellular Metabolism	K-P. Huang
Z01 HD 00188-02	Development of New Analogs of Enkephalin with Increased Receptor Activity and Selectivity	D. Rodbard
Z01 HD 00189-01	Development of Statistical Software For Use By Clinical and Laboratory Investigation.....	D. Rodbard

ANNUAL REPORT
of the
Endocrinology and Reproduction Research Branch
National Institute of Child Health and Human Development
October 1, 1981 through September 30, 1982

The research programs of the Endocrinology and Reproduction Research Branch are directed at the elucidation of mechanisms responsible for hormone secretion and action, and at the investigation of normal and disordered function of the hypothalamic-pituitary system and its effects upon gonadal and adrenal function. These programs include studies on the characterization of peptide hormones and transmitters, and their cellular receptors; the structure-function relationships of peptide and glycoprotein hormones; the regulation of hormone biosynthesis and secretion; and the mechanisms of peptide hormone action. Of particular interest are the analysis of pituitary-gonadal relationships, the regulation of ovarian function during the reproductive cycle and pregnancy, and the participation of hormone receptors in the regulation of gonadal function. In the current year, progress has been made in several areas of research on hormone secretion and action, and on the receptor-mediated processes that are responsible for the control of steroid production in endocrine target cells. The role of hormones in cellular regulation has also been examined in selected areas of normal and disordered human endocrine function, and in appropriate animal model systems for the analysis of peptide secretion and actions upon the stimulatory and inhibitory control of target-cell function.

The Section on Biophysical Endocrinology conducts research on the mathematical and statistical evaluation of endocrine regulatory processes and the properties of protein hormones and other ligands, studied by electrophoretic techniques, mathematical modeling, computer stimulation, and biophysical methods, during analysis of ligand-receptor interactions, regulation of the ovarian cycle, and cardiovascular changes in thyroid disease. Current studies have included the further development of computer programs for analysis and optimization of radioligand assays, including automatic calculation of weighting coefficients and quality control results. New methods of statistical computing for use by clinical and laboratory investigators are being developed to provide automatic testing of assumptions, and advice on the selection of appropriate statistical procedures to avoid pitfalls in data analysis and interpretation. Mathematical models for the description of hormone-receptor interactions and response coupling were applied to biological systems, including binding of glucocorticoids, opiates, GABA and glutamate to their respective receptors. Of special interest are the cases of multiple ligands interacting with multiple classes of receptors, and of interactions between divalent ligands and cellular receptors. New dimeric analogs of enkephalin were synthesized and shown to be highly potent and specific for the "delta" opiate receptor. Such ligands appear to bind simultaneously to two receptor sites, and may provide an approach for development of supra-active opiate agonists and possibly specific antagonists to the effects of enkephalins. Other studies included the hormonal control of ovarian proteoglycan synthesis by gonadotropins and steroids, the application of measurement of the QKd interval for monitoring thyroid function in man, and the role of regional body temperature in the pathogenesis of several disease states.

The Electrophoresis Unit conducts research on the development and application of electrophoretic techniques for the fractionation and isolation of peptides and proteins of biological interest. Methods such as analytical polyacrylamide gel electrophoresis (PAGE), electrofocusing, and isotachopheresis are employed for the characterization and isolation of hormonal and other regulatory proteins. Recent research has focused on the development of improved methods for electrofocusing, including the prediction and measurement of pH gradients, clarification of the applicability of moving boundary electrophoresis theory to current separation methods including isotachopheresis, multiphasic zone electrophoresis and isoelectrofocusing, the use of hydroxyethylated agarose in moving boundary electrophoresis, and the exclusive regulation of voltage across the gel during electrofocusing of thermolabile proteins. These techniques were applied to the analysis of glucocorticoid receptors of the developing chick neural retina, which was comprised of at least three binding species. Changes in the proportions of these components were observed during temperature-induced activation of the glucocorticoid receptor. Other studies included approaches to the preparative isolation of hGH from genetically-transformed bacterial cultures, and to the molecular characterization of the components of the renin-angiotensin-aldosterone system.

The Section on Molecular Structure conducts research on the analysis, synthesis, and structure-function relationships of biologically active peptides. This includes the identification and synthesis of unusual structure and sequences in amino acids and peptides, and the development of new techniques for peptide sequencing and synthesis. Correlations between peptide structure and function are analyzed in hypothalamic releasing hormones, including gonadotropin-releasing hormone (GnRH) and the recently discovered corticotropin-releasing factor (CRF) described by Vale and colleagues. The 41 amino acid CRF molecule has been synthesized in high yield and shown to be of high activity on ACTH release in cultured pituitary cells. Fragments of the molecule have been prepared for structure-function studies, and modified sequences will be synthesized for potential super-agonist or antagonist activities. New techniques for peptide synthesis include the use of selenophenol as a deprotecting agent. Other peptides synthesized and studied include a renin-inhibitory peptide, cholecystokinin, and partial sequences of viral peptides for use in producing specific antibodies.

The Protein Chemistry Unit conducts research on the chemical and biological properties of gonadotropins in tissues and body fluids, with emphasis on the isolation, structure-function relationships, and assay of gonadotropins. Previous studies have demonstrated the presence of an hCG-like hormone (hCG') in the human pituitary gland, with physicochemical, immunological, and biological features typical of hCG. The pituitary gland contains the highest amount of hCG' among non-pregnant tissues, suggesting that the hCG-like hormone could be a precursor of LH in the human pituitary gland. Current studies revealed a wide correlation in the hCG' content of human pituitary gland, and a less variable content of hLH, with no direct correlation between hLH and hCG' content. The hCG-like substance was also detected during the luteal phase in 3 women bearing IUDs, though not in cycles from 4 normal women. In studies on hCG itself, chromatofocusing was employed to analyze the charge heterogeneity of urinary hCG from pregnant women and patients with trophoblastic disease. The hCG profiles during normal pregnancy, and in molar pregnancy or choriocarcinoma, were similar to that of purified hCG from pregnancy urine. However, hCG in patients with toxemia of pregnancy differed in that its predominant components were relatively less acidic. Studies on the role of carbohydrate moieties in the biological activity were consistent with the possibility that the β -subunit and its carbohydrate components are of major importance in determining in vivo bioactivity of the hCG molecule. In the area

of peptide synthesis, the search for δ -specific enkephalin derivatives has led to the identification of a tetrapeptide dimer with high selectivity for the δ -opiate receptor.

The Metabolism Unit studies the regulation and hormonal control of glycogen metabolism in normal and diabetic tissues, and the mechanisms by which protein kinase and phosphoprotein phosphatase regulate the activity of glycogen synthase. In recent studies, the dephosphorylated form of rat liver glycogen synthase was purified and shown to be phosphorylated by both cAMP-dependent and independent protein kinases without loss of activity, in contrast to skeletal muscle synthase. However, the liver enzyme was inactivated when phosphorylated first by cAMP-dependent protein kinase, followed by cAMP-independent casein kinase. Prior phosphorylation of glycogen synthase by the former enzymes caused an enhanced rate of phosphorylation by casein kinase 1. The phosphorylation by cAMP-dependent protein kinase and phosphorylase kinase was found to involve a common site which differed from those phosphorylated by casein kinases 1 and 2. An antibody was raised against the purified synthase from normal liver and shown to cross-react less well with synthase from diabetic rat liver, suggesting an immunological difference between the two states of the enzyme. The cAMP-independent casein kinase 1 from skeletal muscle was found to phosphorylate several muscle proteins (eg, troponin, myosin light chain and its kinase) in addition to glycogen synthase and phosphorylase kinase, suggesting that this enzyme (like cAMP-dependent protein kinase) may have multiple cellular functions. Also, the sites at which muscle casein kinase 2 phosphorylated glycogen synthase, troponin, and myosin light chain, were shown to differ from those phosphorylated by casein kinase 1.

The Section on Molecular Endocrinology investigates the molecular basis of peptide hormone action, with particular emphasis on the characterization of gonadotropin receptors, activation of steroid biosynthesis in gonads and adrenal, and analysis of the biological activity of circulating gonadotropins. Recent studies on the mechanism of action of LH-like gonadotropins in the testis have shown that the cyclic AMP-mediated responses of the Leydig cell to LH or hCG depend upon activation of a protein kinase with chromatographic characteristics of the Type I enzyme, but with functional properties more similar to the Type II enzyme of bovine myocardium. The action of hCG on testicular androgen secretion is accompanied and/or followed by the appearance of steroidogenic lesions of the late biosynthetic pathway (17 α -hydroxylase, 17-20 desmolase) that appear to be estrogen-dependent. Studies in vitro have shown that a protein of MW 27,000 is induced by estradiol in cultured Leydig cells, and possibly mediates the inhibitory effects of estradiol and hCG upon the microsomal enzymes responsible for conversion of progesterone to androgens. An additional early steroidogenic lesion in hCG-stimulated Leydig cells was shown to be in part due to impaired activity of the rate-limiting enzyme, HMG-CoA reductase. Studies performed in 4-APP-treated rats to define this early lesion also showed that this agent decreased LH secretion, and that this effect of 4-APP, rather than its inhibition of hepatic lipoprotein production, is responsible for the concomitant decrease in testosterone secretion. Analysis of rat interstitial cells by density gradient fractionation revealed that the most dense Leydig cells were the most responsive to gonadotropin stimulation, and that lighter Leydig cell fractions were morphologically damaged as well as functionally unresponsive to gonadotropins. In cultured fetal Leydig cells, the actions of gonadotropins on LH receptor regulation and steroid responses were found to differ from those in the adult, in that no receptor loss or desensitization of androgen responses was seen in the fetal cells. In adult Leydig cells, studies on the effects of LH on adenylate cyclase were continued, with analysis of membrane-phosphorylation and guanyl nucleotide binding during hormone action.

These studies suggested that phosphorylation of the guanyl nucleotide regulatory protein may be involved in the control of adenylate cyclase activity, and that this process is modulated by changes in calcium availability. The ability of dispersed Leydig cells to provide a sensitive bioassay for serum LH was applied to studies on circulating LH in men and post-menopausal women, which indicated that LH is secreted in pulses of high biological activity. This work has also demonstrated that the bioactivity of secreted LH is influenced by gonadal steroids in man, rhesus monkey, and rat.

The Section on Hormonal Regulation performs research on the control of endocrine target cells by peptide hormones, in particular the characterization, regulation, and activation mechanisms of membrane receptors for gonadotropins, lactogens, angiotensin, and gonadotropin-releasing hormone (GnRH). Current studies on testicular regulation have defined the changes in sensitivity of the rat Leydig cell to gonadotropin stimulation during sexual maturation. These include loss of the trophic response of LH receptors and steroidogenic capacity to gonadotropins, with acquisition of the adult-type responses of receptor down-regulation and desensitization of androgen production during the replacement of the fetal Leydig cell population by those of the adult testis. This transition in Leydig-cell responses may also be related to the appearance of detectable estrogen receptors in the testis after the first week of life, as well as to differences in the rates of membrane and receptor turnover in fetal and adult Leydig cell populations. In the adult Leydig cell, in vivo studies revealed that occupancy of only a few receptors, 5 or less per cell, was sufficient to elicit a steroidogenic response, and that about 99% of the LH sites are spare or in excess of the number needed to maximally stimulate androgen secretion. In studies on ovarian granulosa cells, the action of FSH on cellular maturation was shown to be mediated by cyclic AMP, and the direct inhibitory actions of GnRH agonists on follicle development were found to depend upon impairment of cyclic AMP production. Ovarian receptors for GnRH were shown to mediate the inhibitory actions of GnRH agonists, as well as their less prominent stimulatory effects upon ovarian function.

In studies on the control of gonadotropin secretion, rat pituitary GnRH receptors were shown to be positively regulated by exogenous or endogenous GnRH, and to provide a useful index of endogenous GnRH secretion. GnRH agonist analogs were shown to be bound by pituitary cells in proportion to their receptor binding affinities, and resistance to degradation was a minor factor at the target-cell level. GnRH receptors and actions were characterized in gonadotrophs purified by unit gravity sedimentation and centrifugal elutriation, and the latter method was shown to be of particular value for preparing fractions enriched in lactotrophs or gonadotrophs. Up-regulation of GnRH receptors was demonstrated in cultured pituitary cells, and stimulation and desensitization by GnRH was studied in perfused pituitary cells. Further evidence for the role of phospholipid turnover and arachidonic acid metabolites in GnRH action was obtained in pituitary gonadotrophs. In the corticotroph, studies on the interaction between synthetic CRF and other regulators of cyclic AMP and corticotropin secretion were performed. In the lactotroph, receptors for angiotensin II (AII) were identified and shown to mediate a stimulatory effect of the octapeptide upon prolactin release in vitro.

In studies on the actions of AII and other factors on aldosterone secretion, the adrenal and vascular sites for AII were shown to undergo reciprocal regulation during changes in sodium balance, in keeping with the concomitant changes in

vascular and adrenal sensitivity for AII. The effects of AII on aldosterone secretion were found to be selectively inhibited by somatostatin, for which high-affinity receptors were identified and characterized in the rat zona glomerulosa. The role of calcium in the steroidogenic action of AII was further analyzed by ionophore studies which indicated that changes in cytosolic calcium lead to stimulation of aldosterone production by glomerulosa cells. Other studies were initiated on the dopaminergic control of aldosterone secretion, and the characteristics of AII receptors in the human adrenal gland.

The Adrenal Research Unit investigates the physiology and regulation of adrenal steroidogenesis, by characterization of cellular steroid-binding proteins and soluble factors which mediate steroidogenic responses to ACTH, and analysis of cellular mechanisms of cholesterol utilization in steroid biosynthesis. Current research has employed the guinea pig as a model for analyzing the differential function of the adrenocortical zones. Although the outer (fasciculata plus glomerulosa) zone contains up to 100 times more cortisol than the inner (reticularis) zone, the two regions show similar cortisol production after homogenization and incubation, suggesting that the intact inner zone may be metabolizing cortisol more rapidly, or is perhaps inhibited from producing cortisol. Differential production of adrenal androgens was also observed, with a higher content of DHA (but no androstenedione) in the inner zone. The major steroid sulfate in the guinea pig adrenal was pregnenolone sulfate, rather than DHA sulfate as in primates. These studies will be extended to analyze the relationships between reticularis and fasciculata zones during the regulation of adrenal corticosteroid and androgen synthesis. The specific proteins involved in steroid biosynthesis were further studied with identification of two species of cholesterol-binding proteins (16S and 2S). The former is heat-labile and calcium-inhibited, and the appearance of the latter is dependent on heat and low pH. Specific binding proteins for pregnenolone (MW 34,000) and pregnenolone sulfate were also characterized. The role of these proteins which serve to bind the substrate and products of the side-chain cleavage enzyme will be further analyzed during the physiological control of steroidogenesis in adrenocortical cells.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00022-09 RR	
PERIOD COVERED October 1, 1981 - September 30, 1982			
TITLE OF PROJECT (80 characters or less) Renin-Angiotensin System and Aldosterone Regulation			
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT			
PI:	A. Aguilera K. J. Catt	Visiting Scientist Chief	ERRB, NICHD ERRB, NICHD
Others:	J. Fakunding J. Wilson	Staff Fellow Guest Worker	ERRB, NICHD ERRB, NICHD
COOPERATING UNITS (if any) J. Gill, Hypertension - Endocrine Branch, NHLBI.			
LAB/BRANCH Endocrinology and Reproduction Research Branch			
SECTION Section on Hormonal Regulation			
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205			
TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.0	OTHER: 1.0	
CHECK APPROPRIATE BOX(ES)			
<input type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER			
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS			
SUMMARY OF WORK (200 words or less - underline keywords) The purpose of this work is to investigate physiological and pathological aspects of the <u>renin-angiotensin system</u> , with emphasis on the <u>regulation of aldosterone secretion by the zona glomerulosa of the adrenal gland</u> . Specific topics include the characterization and regulation of <u>angiotensin II (AII) receptors</u> , the actions of AII and other regulators of aldosterone secretion, the production and <u>metabolism of AII</u> , and the use of enzyme-dispersed <u>adrenal cells</u> for analysis of the relations between AII receptors and aldosterone production. These studies have shown that vascular and adrenal receptors from AII undergo reciprocal regulation during changes in <u>sodium balance</u> , in keeping with the concomitant changes in vascular and adrenal sensitivity for AII. The effects of AII on aldosterone secretion were found to be selectively inhibited by <u>somatostatin</u> , for which high-affinity receptors were identified and characterized in the rat zona glomerulosa. The role of <u>calcium</u> in the steroidogenic action of AII was further analyzed by ionophore studies which indicated that changes in cytosolic calcium lead to stimulation of aldosterone production by glomerulosa cells. Other studies were initiated on the <u>dopaminergic control of aldosterone secretion</u> , and the characteristics of AII receptors in the human adrenal gland.			

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00035-10 RR
PERIOD COVERED October 1, 1981 - September 30, 1982		
TITLE OF PROJECT (80 characters or less) The Structure and Function of Biologically Active Molecules		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: J. L. Morell Research Chemist, SMS ERRB-NICHD Other: P. Gaudreau Guest Worker ERRB-NICHD		
COOPERATING UNITS (if any) C. B. Pert, NIMH, Bethesda, MD. H. Westphal, NICHD, Bethesda, MD.		
LAB/BRANCH Endocrinology and Reproduction Research Branch SECTION Section on Molecular Structure		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.0	OTHER: 1.0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) These studies are directed toward the analysis and synthesis of molecular assemblies with common and rare amino acids including: 1) preparation of analogs of <u>Corticotropin Releasing Factor</u> with "unnatural amino acids" in a search for antagonists or prolongation of activity; 2) preparation of fragments of Corticotropin Releasing Factor for determination of structures necessary for binding to its receptors; 3) development of new techniques in peptide synthesis including use of <u>selenophenol</u> as a deprotecting agent; 4) <u>large scale preparation</u> of hormones such as Corticotropin Releasing Factor and <u>renin inhibitor</u> for clinical use; 5) combinations of <u>α,β-unsaturated amino acids</u> with nucleotides such as 5-aminoimidazole-4-(N-fumarylcarboxamide) ribotide and adenylofumarate, to study their action on <u>neoplastic tissue</u> and <u>viral replication</u> ; 6) partial sequences of <u>cholecystokinin</u> and correlation of structure with function; 7) preparation of partial sequences of viral peptides and conjugation with carriers for the purpose of producing antibodies.		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00040-07 RR																																				
PERIOD COVERED October 1, 1981 - September 30, 1982																																						
TITLE OF PROJECT (80 characters or less) Experimental and Theoretical Studies of Hormone Receptor Interaction and Response Coupling.																																						
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0" style="width: 100%;"> <tr> <td style="width: 10%;">PI</td> <td style="width: 30%;">P. J. Munson</td> <td style="width: 40%;">Mathematician-Statistician</td> <td style="width: 20%;">ERRB, NICHD</td> </tr> <tr> <td></td> <td>D. Rodbard</td> <td>Head, Section on Biophysical Endocrinology</td> <td>ERRB, NICHD</td> </tr> <tr> <td></td> <td>S. Krumins</td> <td>Visiting Fellow</td> <td>ERRB, NICHD</td> </tr> <tr> <td></td> <td>T. Costa</td> <td>Visiting Fellow</td> <td>ERRB, NICHD</td> </tr> <tr> <td>Others</td> <td>D. Shafer</td> <td>Clinical Associate</td> <td>NIAMDD</td> </tr> <tr> <td></td> <td>E. A. Jones</td> <td>Branch Chief</td> <td>NIAMDD</td> </tr> <tr> <td></td> <td>G. P. Chrousos</td> <td></td> <td>DEB, NICHD</td> </tr> <tr> <td></td> <td>D. Brandon</td> <td></td> <td>DEB, NICHD</td> </tr> <tr> <td></td> <td>H. M. Schulte</td> <td>Visiting Fellow</td> <td>DEB, NICHD</td> </tr> </table>			PI	P. J. Munson	Mathematician-Statistician	ERRB, NICHD		D. Rodbard	Head, Section on Biophysical Endocrinology	ERRB, NICHD		S. Krumins	Visiting Fellow	ERRB, NICHD		T. Costa	Visiting Fellow	ERRB, NICHD	Others	D. Shafer	Clinical Associate	NIAMDD		E. A. Jones	Branch Chief	NIAMDD		G. P. Chrousos		DEB, NICHD		D. Brandon		DEB, NICHD		H. M. Schulte	Visiting Fellow	DEB, NICHD
PI	P. J. Munson	Mathematician-Statistician	ERRB, NICHD																																			
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Others	D. Shafer	Clinical Associate	NIAMDD																																			
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	G. P. Chrousos		DEB, NICHD																																			
	D. Brandon		DEB, NICHD																																			
	H. M. Schulte	Visiting Fellow	DEB, NICHD																																			
COOPERATING UNITS (if any)																																						
LAB/BRANCH Endocrinology and Reproduction Research Branch																																						
SECTION Biophysical Endocrinology																																						
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205																																						
TOTAL MANYEARS: 2.5	PROFESSIONAL: 2.5	OTHER:																																				
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																																						
SUMMARY OF WORK (200 words or less - underline keywords) This project includes a continuing series of theoretical studies and analysis of experiments regarding hormone receptor interactions. The theoretical studies seek to develop appropriate mathematical models for the description of hormone-receptor interactions and response couplings. A variety of model biological systems have been used to develop and test these mathematical models such as opiate binding to its receptors, glucocorticoid binding to receptors, GABA and muscimol binding, and glutamate binding. By development of appropriate mathematical models and computer programs for curve fitting and data analysis we have been able to characterize several of these ligand receptor systems. Special attention has been given to the case of multiple ligands reacting simultaneously with multiple classes of sites and the interaction of divalent ligands with cell surface receptors.																																						

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00041-07 RR								
PERIOD COVERED October 1, 1981 - September 30, 1982										
TITLE OF PROJECT (80 characters or less) Cardiovascular Effects of Thyroid, Hormones, Catecholamines and Cardiotoxic Drugs.										
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0" style="width: 100%;"> <tr> <td style="width: 10%;">PI</td> <td style="width: 30%;">D. Rodbard</td> <td style="width: 40%;">Head, Section on Biophysical Endocrinology</td> <td style="width: 20%;">ERRB, NICHD</td> </tr> <tr> <td>Other</td> <td>R. Osburn E. C. Ridgway</td> <td>Professor, Thyroid Unit</td> <td>NNMC Massachusetts</td> </tr> </table>			PI	D. Rodbard	Head, Section on Biophysical Endocrinology	ERRB, NICHD	Other	R. Osburn E. C. Ridgway	Professor, Thyroid Unit	NNMC Massachusetts
PI	D. Rodbard	Head, Section on Biophysical Endocrinology	ERRB, NICHD							
Other	R. Osburn E. C. Ridgway	Professor, Thyroid Unit	NNMC Massachusetts							
COOPERATING UNITS (if any) National Naval Medical Center, Bethesda, Maryland Massachusetts General Hospital, Boston, Massachusetts.										
LAB/BRANCH Endocrinology and Reproduction Research Branch										
SECTION Biophysical Endocrinology										
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205										
TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.5	OTHER:								
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS										
SUMMARY OF WORK (200 words or less - underline keywords) The pulse wave arrival time (designated QK_d), has been further demonstrated to be useful in evaluating thyroid function under conditions of "diminished thyroid reserve", and in the evaluation of the changes in thyroid hormones which occur during hypocaloric feeding in humans. The QK_d has been used to demonstrate that supplementation with oral thyroxin results in improvement at the target organ level, in patients with diminished thyroid reserve as manifested by low or borderline low thyroid function with moderate or minimal TSH elevation. In human subjects undergoing prolonged hypocaloric feeding, normally there is a decrease in serum T4 and T3. Under this set of circumstances, the QK_d is prolonged, suggestive of hypothyroidism at the target organ level. Further, oral supplementation with T3, to maintain a euthyroid level of T3, prevents the changes in QK_d . In contrast, oral supplementation with T4 which results in supra-normal levels of T4 but slightly decreased levels of T3, fails to provide complete return to normal of the QK_d . These findings suggest that QK_d is more closely correlated with T3 than with T4 levels, and further suggests that the changes observed in peripheral thyroid hormones levels during hypocaloric feeding is indeed an adaptive mechanism which results in a state of hypometabolism.										

PERIOD COVERED
 October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)
 Mathematics and Statistics of Radioligand Assays.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI	D. Rodbard	Head, Section on Biophysical Endocrinology	ERRB, NICHD
	Peter Munson	Mathematical-Statistician	ERRB, NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
 Endocrinology and Reproduction Research Branch

SECTION
 Biophysical Endocrinology

INSTITUTE AND LOCATION
 NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS
 (b) HUMAN TISSUES
 (c) NEITHER

(a1) MINORS
 (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The mathematical and statistical theories of radioimmunoassay and related techniques have been under development. We have been interested in the enzyme multiplied immunological technique (EMIT), the enzyme-linked-immuno-adsorbent assay (ELISA), and the chemiluminescent assays. The mathematical theory of optimization of RIA, and appropriate computer programs have been further developed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 HD 00146-07 RR

PERIOD COVERED

October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)

Structure and Function of Chorionic Gonadotropins

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI	H. C. Chen	Senior Investigator	ERRB, NICHD
OTHERS:	S. C. Huang	Visiting Associate	ERRB, NICHD
	Y. Shimohigashi	Visiting Fellow	ERRB, NICHD

COOPERATING UNITS (if any)

A.S. Hartree, Agricultural Research Council, Cambridge, England
P.C. Ouyang, National Taiwan University Hospital, Taipei, Taiwan

LAB/BRANCH

Endocrinology and Reproduction Research Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:

2.8

PROFESSIONAL:

2.8

OTHER:

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS

(b) HUMAN TISSUES

(c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The topics of this project are to study the chemical, immunological and biological properties of gonadotropins in tissues and biological fluids of normal subjects and patients with neoplasms. A simple peptide model is employed in the structure-function studies of hormones. Specifically, evidence has been accumulated to indicate the presence of human chorionic gonadotropin (hCG) or hCG-like substance distinct from the luteinizing hormone in the pituitary glands and in urines collected during the late luteal phase from women receiving contraceptive measures. A simple and effective analytical method to detect alteration of hCG glycosylation in toxemia patient was developed, and the dominant role of carbohydrate structure in the β -subunit of hCG was elucidated. Finally, a series of δ -opiate receptor specific enkephalin peptides were synthesized.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00147-07 RR
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PERIOD COVERED
October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)
Mechanism of Action of Peptide Hormones in Steroidogenic Cells

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI	Maria L. Dufau	Chief, Section on Molecular Endocrinology	ERRB, NICHD
	Kevin J. Catt	Chief	ERRB, NICHD
Other	K. Nozu	Visiting Fellow	ERRB, NICHD
	A. Dehejia	Student Scientist	ERRB, NICHD
	J. L. Baranao	Visiting Fellow	ERRB, NICHD
	M. Hattori	Visiting Fellow	ERRB, NICHD
	D. Warren	Guest Worker	ERRB, NICHD

COOPERATING UNITS (if any)
Primate Research Center, Atlanta, Georgia

LAB/BRANCH
Endocrinology and Reproduction Research Branch

SECTION
Sections on Molecular Endocrinology and Hormonal Regulation

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 4.0	PROFESSIONAL: 3.0	OTHER: 1.0
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The broad goal of this project is to understand the steps involved in the hormonal control of steroidogenesis. This includes the metabolic events that follow stimulation of specific receptors in steroidogenic cells by trophic hormones, including the coupling mechanisms between receptor occupancy and the sequence of events which leads to stimulation or inhibition of steroidogenic enzymes and androgen production. We have a) demonstrated that Leydig cell protein kinase behaves as a Type I enzyme on DEAE analysis, but has physical and functional characteristics that resemble the Type II enzyme of bovine myocardium; b) fractionated and analyzed Leydig cell populations, in which electron microscopic studies suggest that functional Leydig cells are of higher density, probably related to their extensive endoplasmic reticulum and mitochondria. c) established in vitro cultures of adult and fetal Leydig cell and investigated gonadotropin-dependent regulatory mechanisms; d) demonstrated that a 27,000 protein is induced by estradiol and that similar protein is produced in the Leydig cell during hCG stimulation. This protein could in turn serve to regulate microsomal enzymatic activities.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 HD 00148-07 RR

PERIOD COVERED

October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)

Ontogeny of Gonadotropin Receptors and Gonadal Function

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K. J. Catt	Chief, ERRB	ERRB, NICHD
	M. L. Dufau	Chief, SME	ERRB, NICHD
Others:	L. Huhtaniemi	Visiting Scientist	ERRB, NICHD
	D. Warren	Guest Worker	UCLA

COOPERATING UNITS (if any)

I. Huhtaniemi, Dept. of Clinical Chemistry, University of Helsinki, Finland.
D. W. Warren, Dept. of Physiology, UCLA.

LAB/BRANCH

Endocrinology and Reproduction Research Branch

SECTION

Section on Hormonal Regulation

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:

1.5

PROFESSIONAL:

1.0

OTHER:

0.5

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) This project is concerned with analysis of the developmental characteristics of gonadotropin receptors during fetal life and sexual maturation. Studies are performed on the emergence of receptors and biochemical responses of the pituitary-gonadal system during development, on the maturation of testicular and ovarian endocrine function, and on the control of gonadal sensitivity during sexual maturation. The current studies have defined the changes in sensitivity to gonadotropin stimulation that occur in the rat Leydig cell during early development. These changes include a progressive loss of the trophic response to gonadotropins, with acquisition of the adult-type response after about 20 days of age, the latter being characterized by a period of refractoriness after the initial stimulation of Leydig-cell function. This temporary phase of testicular desensitization is due to loss of LH receptors and lesions of the steroidogenic pathway which are in part attributable to an estrogen-mediated consequence of increased androgen biosynthesis. The absence of these changes in the fetal and neonatal testis may be related to the lack of detectable estrogen receptors in the first several days of life, and to differences in the rates of turnover of membrane receptors between the fetal and adult Leydig cell populations.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00149-07 RR
PERIOD COVERED October 1, 1981 - September 30, 1982		
TITLE OF PROJECT (80 characters or less) Bioassay of Serum Luteinizing Hormone (LH) and Chorionic Gonadotropin		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI Maria L. Dufau Chief, Section on Molecular ERRB, NICHD		
COOPERATING UNITS (if any) Dept. of Gynecology, Mass. General Hospital, Boston, Mass.: Primate Research Center, Atlanta, Georgia; Department of Medicine, University of Rome, Italy; Dept. of Pathology, University of New Mexico; Utah State University.		
LAB/BRANCH Endocrinology and Reproduction Research Branch		
SECTION Section on Molecular Endocrinology		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 1.2	PROFESSIONAL: 0.2	OTHER: 1.0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Long range studies on the <u>in vitro</u> bioactivity of <u>luteinizing</u> hormone and <u>chorionic gonadotropin</u> in man and other species were continued. The recently <u>in vitro</u> bioassay for the measurement of LH and hCG in serum has been more extensively applied to studies on gonadotropin regulation in <u>man</u> and <u>other species</u> . Studies on the <u>pulsatile</u> release of LH in <u>men</u> and <u>postmenopausal female</u> have demonstrated the value of <u>bioactive LH</u> determinations to analyze serum LH profiles, and indicated that LH is secreted in <u>pulses</u> of <u>high biological activity</u> .		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00150-07 RK
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PERIOD COVERED October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)
Characterization and Purification of LH/hCG Receptors and Adenylate Cyclase

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: M. L. Dufau	Chief, Section on Molecular Endocrinology	ERRB, NICHD
K. J. Catt	Chief	ERRB, NICHD

COOPERATING UNITS (if any)
None

LAB/BRANCH
Endocrinology and Reproduction Research Branch

SECTION
Section on Molecular Endocrinology

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.7	PROFESSIONAL: 0.1	OTHER: 0.6
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CHECK APPROPRIATE BOX(ES)
 (a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER
 (a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is concerned with solubilization, characterization and purification of gonadotropin and prolactin receptors and adenylate cyclase of testis and ovary. In addition to analyzing the properties of gonadotropin receptors and adenylate cyclase, and of the physical and functional relationships of the binding site and the enzyme complex in the cell membrane and in solution.

Recent findings suggest that phosphorylation of the guanyl nucleotide regula-
tory protein mediates activation of adenylate cyclase during hormone action,
and that this process can be modulated by changes in calcium availability.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00151-07 RR																
PERIOD COVERED October 1, 1981 - September 30, 1982																		
TITLE OF PROJECT (80 characters or less) Receptor-mediated regulation of gonadal function																		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0" style="width: 100%;"> <tr> <td style="width: 10%;">PI:</td> <td style="width: 40%;">K. J. Catt</td> <td style="width: 30%;">Chief, ERRB</td> <td style="width: 20%;">ERRB, NICHD</td> </tr> <tr> <td></td> <td>M. L. Dufau</td> <td>Chief, ERRB</td> <td>ERRB, NICHD</td> </tr> <tr> <td>Others:</td> <td>M. Knecht</td> <td>Staff Fellow</td> <td>ERRB, NICHD</td> </tr> <tr> <td></td> <td>T. Ranta</td> <td>Guest Worker</td> <td>ERRB, NICHD</td> </tr> </table>			PI:	K. J. Catt	Chief, ERRB	ERRB, NICHD		M. L. Dufau	Chief, ERRB	ERRB, NICHD	Others:	M. Knecht	Staff Fellow	ERRB, NICHD		T. Ranta	Guest Worker	ERRB, NICHD
PI:	K. J. Catt	Chief, ERRB	ERRB, NICHD															
	M. L. Dufau	Chief, ERRB	ERRB, NICHD															
Others:	M. Knecht	Staff Fellow	ERRB, NICHD															
	T. Ranta	Guest Worker	ERRB, NICHD															
COOPERATING UNITS (if any) I. Huhtaniemi, Dept. of Clinical Chemistry, University of Helsinki, Finland.																		
LAB/BRANCH Endocrinology and Reproduction Research Branch																		
SECTION Section on Hormonal Regulation																		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205																		
TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.5	OTHER: 0.5																
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																		
SUMMARY OF WORK (200 words or less - underline keywords) This program is directed at the analysis of peptide hormone receptors in <u>testis</u> and <u>ovary</u> , with particular reference to the control of <u>receptor concentration</u> by changes in <u>homologous</u> and <u>heterologous hormones</u> . <u>Desensitization</u> of gonadal <u>adenylate cyclase</u> and <u>steroidogenic responses</u> by <u>gonadotropic hormones</u> is followed by <u>receptor loss</u> and turnover or processing of the <u>hormone-receptor complex</u> . These processes are investigated in <u>Leydig cells</u> and <u>ovarian granulosa cells</u> to determine the effects of hormone-induced <u>receptor regulation</u> on gonadal responsiveness, and to analyze the mechanism and consequences of <u>target-cell desensitization</u> . The receptors and direct actions of <u>gonadotropin-releasing hormone</u> (GnRH) in the ovary and testis are also analyzed. The effects of <u>FSH</u> on granulosa-cell maturation were shown to be mediated by <u>cyclic AMP</u> , and the inhibitory actions of <u>GnRH agonists</u> on this process were associated with decreased cAMP production. <u>GnRH receptors</u> in the granulosa cell were shown to mediate the minor stimulatory effects of GnRH on <u>ovarian function</u> , as well as the more prominent <u>anti-gonadal</u> actions of GnRH in the ovary.																		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00160-07 RR
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PERIOD COVERED
October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)
Biology of the Adrenal Cortex: Development and Regulation of Cellular Zonation; Molecular Events in Steroid Biosynthesis and Secretion

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI	Charles A. Strott	Senior Investigator	ERRB, NICHD
Other	Tetsuo Nishikawa	Visiting Fellow	ERRB, NICHD
	Takao Obara	Visiting Fellow	ERRB, NICHD

COOPERATING UNITS (if any)
None

LAB/BRANCH
Endocrinology and Reproduction Research Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 4	PROFESSIONAL: 3	OTHER: 1
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The long-term aim of this project is to explore in depth the biology of the adrenal cortex with emphasis on biochemical and biophysical events surrounding steroid synthesis and secretion. There are numerous areas of uncertainty as to the molecular events involving: 1) initiation, propagation, and termination of steroid synthesis; 2) intercompartmental movement of steroid precursors and intermediates; 3) secretion of steroid products. Additional areas of importance which will require extensive experimentation are: 1) the interaction of subcellular organelles such as mitochondria, endoplasmic reticulum, Golgi apparatus, microtubules, microfilaments, lipid droplets, etc.; 2) Soluble factors which influence the steroidogenic process; 3) cell-cell interactions or zone-zone interactions (specific cells in certain regions or zones of the cortex exhibit distinct functional differences); 4) The life span and turnover of adrenocortical cells including the concept of cell migration. Current areas of research deal with 1) differential function of the outer and inner cortical zones, 2) biochemistry and physiology of soluble steroid-binding proteins, 3) investigation of soluble stimulatory and inhibitory factors, 4) examination of adrenocortical secretory proteins.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00165-07 RR																																
PERIOD COVERED October 1, 1981 - September 30, 1982																																		
TITLE OF PROJECT (80 characters or less) Isolation and Characterization of Protein Hormones and Other Active Proteins																																		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0"> <tr> <td data-bbox="69 419 145 449">PI</td> <td data-bbox="230 419 429 449">A. Chrambach</td> <td data-bbox="521 419 827 449">Senior Investigator</td> <td data-bbox="987 419 1164 449">ERRB, NICHD</td> </tr> <tr> <td data-bbox="69 485 145 516">Other</td> <td data-bbox="230 485 378 516">S. Ben-Or</td> <td data-bbox="521 485 812 516">Visiting Scientist</td> <td data-bbox="972 485 1336 516">The Hebrew University 1</td> </tr> <tr> <td></td> <td data-bbox="230 520 378 550">Zs. Buzas</td> <td data-bbox="521 520 768 550">Visiting Fellow</td> <td data-bbox="972 520 1336 550">University of Szeged 2</td> </tr> <tr> <td></td> <td data-bbox="230 554 364 584">A. Jones</td> <td data-bbox="521 554 827 584">Research Biochemist</td> <td data-bbox="972 554 1249 584">Genentech, Inc. 3</td> </tr> <tr> <td></td> <td data-bbox="230 588 393 618">G. Kapadia</td> <td data-bbox="521 588 713 618">Guest Worker</td> <td></td> </tr> <tr> <td></td> <td data-bbox="230 622 364 653">C. Auzan</td> <td data-bbox="521 622 666 653">Assistant</td> <td data-bbox="972 622 1263 653">INSERM Unite 36 4</td> </tr> <tr> <td></td> <td data-bbox="230 657 407 687">M. E. Oblin</td> <td data-bbox="521 657 713 687">Investigator</td> <td data-bbox="1004 657 1019 687">"</td> </tr> <tr> <td></td> <td data-bbox="230 691 378 721">P. Corvol</td> <td data-bbox="521 691 666 721">Professor</td> <td data-bbox="1004 691 1019 721">"</td> </tr> </table>			PI	A. Chrambach	Senior Investigator	ERRB, NICHD	Other	S. Ben-Or	Visiting Scientist	The Hebrew University 1		Zs. Buzas	Visiting Fellow	University of Szeged 2		A. Jones	Research Biochemist	Genentech, Inc. 3		G. Kapadia	Guest Worker			C. Auzan	Assistant	INSERM Unite 36 4		M. E. Oblin	Investigator	"		P. Corvol	Professor	"
PI	A. Chrambach	Senior Investigator	ERRB, NICHD																															
Other	S. Ben-Or	Visiting Scientist	The Hebrew University 1																															
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	C. Auzan	Assistant	INSERM Unite 36 4																															
	M. E. Oblin	Investigator	"																															
	P. Corvol	Professor	"																															
COOPERATING UNITS (if any) 1) Department of Physiology, Hadassah Medical School, The Hebrew University, Jerusalem, Israel; 2) Department of Biochemistry, University of Szeged, Szeged, Hungary; 3) Genentech Inc., San Francisco, CA; 4) INSERM, Unite 36, 17, one de Fer-a-Moulau, Paris, France.																																		
LAB/BRANCH Endocrinology and Reproduction Research Branch																																		
SECTION Office of the Chief																																		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205																																		
TOTAL MANYEARS: 2	PROFESSIONAL: 2	OTHER:																																
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																																		
SUMMARY OF WORK (200 words or less - underline keywords) 1) <u>Glucocorticoid receptor</u> quantitatively recovered from electrofocusing on Sephadex consists of at least 3 protein <u>components</u> . Temperature dependent activation of the receptor is concomitant with a <u>specific transformation</u> among those compounds. 2) Human growth hormone (hGH) produced by <u>genetically modified bacterial cells</u> was preparatively separated from bacterial proteins, using moving boundary electrophoresis to extract and concentrate the protein from gel slices. 3) The hydrolysis products of <u>angiotensinogen</u> reacted with renin; native and denatured forms of <u>renin</u> ; angiotensin I to III were separated by Quantitative PAGE. <u>Aldosterone receptor</u> was fractionated by electrofocusing on Sephadex.																																		

PERIOD COVERED

October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)

Other PAGE Instrument and Procedures

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI	A. Chrambach	Senior Investigator	ERRB, NICHD
Other	Zs. Buzas	Visiting Scientist	University of Szeded 1
	S. Ben-Or	Visiting Scientist	The Hebrew University 2
	T. M. Jovin	Section Chief	Max Planck Institute for Physical Chemistry 3
	L. M. Hjelmeland	Collaborator	NEI, NIH

COOPERATING UNITS (if any)

1) As above - 2) As above - 3) Max Planck Institute fur Biophysikalische Chemie,
Gottingen German Federal Republic

LAB/BRANCH

Endocrinology and Reproduction Research Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:

2

PROFESSIONAL:

2

OTHER:

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

1) Electrofocusing is a special case of moving boundary electrophoresis where the common counterion of each constituent is replaced by the solvent ions (proton and hydroxyl ions). 2) The original moving boundary electrophoresis theory of Longworth et al. is a sufficient statement for Steady-State Stacking, Multiphasic zone Electrophoresis and Isotachoporesis, and therefore, abolishes the need for these methodological distinctions, and for their different terminologies. 3) Electroendosmosis-free agarose is compatible with moving boundary electrophoresis of both polarities. 4) Hydroxethylated agarose provides a molecular sieve equivalent to crosslinked polyacrylamide. 5) An apparatus for voltage regulation across the gel exclusively was developed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 HD 00174-06 RR

PERIOD COVERED

October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)

Hormonal Control of Ovarian Proteoglycan Synthesis.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI	D. Rodbard	Head, Section on Biophysical Endocrinology	ERRB, NICHD
	M. Yanagishita	Visiting Fellow	ERRB,
Other	V. C. Hascall	Senior Investigator	LB, NIDR

COOPERATING UNITS (if any)

Laboratory of Biochemistry, NIDR.

LAB/BRANCH

Endocrinology and Reproduction Research Branch

SECTION

Biophysical Endocrinology

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:

1.25

PROFESSIONAL:

1.00

OTHER:

0.25

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS

(b) HUMAN TISSUES

(c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The hormonal factors which stimulate the biosynthesis of proteoglycans by rat ovarian granulosa cells in vitro have been examined in detail. LH, FSH, and HCG have been shown to stimulate proteoglycan synthesis. The identity of these proteoglycans has been determined, and the dose response curves have been characterized. In addition, the effects of estradiol, testosterone, various prostaglandins, and cyclic AMP have been studied in this system. The results provide a necessary background for further studies of the physiology of biosynthesis of ovarian proteoglycans in normal and abnormal states.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00184-04 RR																																
PERIOD COVERED October 1, 1981 - September 30, 1982																																		
TITLE OF PROJECT (80 characters or less) Regulation of Pituitary Hormone Secretion																																		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0" data-bbox="45 469 1348 772"> <tr> <td>PI:</td> <td>Kevin J. Catt</td> <td>Chief, SHR</td> <td>ERRB, NICHD</td> </tr> <tr> <td></td> <td>Greti Aguilera</td> <td>Visiting Scientist</td> <td>ERRB, NICHD</td> </tr> <tr> <td>Others:</td> <td>Ernest Loumaye</td> <td>Visiting Fellow</td> <td>ERRB, NICHD</td> </tr> <tr> <td></td> <td>Camille Hyde</td> <td>Staff Fellow</td> <td>ERRB, NICHD</td> </tr> <tr> <td></td> <td>Ludwig Kiesel</td> <td>Guest Worker</td> <td>ERRB, NICHD</td> </tr> <tr> <td></td> <td>Gunther Emons</td> <td>Guest Worker</td> <td>ERRB, NICHD</td> </tr> <tr> <td></td> <td>Mohan Katikineni</td> <td>Guest Worker</td> <td>ERRB, NICHD</td> </tr> <tr> <td></td> <td>Maria Dufau</td> <td>Chief, SME</td> <td>ERRB, NICHD</td> </tr> </table>			PI:	Kevin J. Catt	Chief, SHR	ERRB, NICHD		Greti Aguilera	Visiting Scientist	ERRB, NICHD	Others:	Ernest Loumaye	Visiting Fellow	ERRB, NICHD		Camille Hyde	Staff Fellow	ERRB, NICHD		Ludwig Kiesel	Guest Worker	ERRB, NICHD		Gunther Emons	Guest Worker	ERRB, NICHD		Mohan Katikineni	Guest Worker	ERRB, NICHD		Maria Dufau	Chief, SME	ERRB, NICHD
PI:	Kevin J. Catt	Chief, SHR	ERRB, NICHD																															
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Others:	Ernest Loumaye	Visiting Fellow	ERRB, NICHD																															
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	Mohan Katikineni	Guest Worker	ERRB, NICHD																															
	Maria Dufau	Chief, SME	ERRB, NICHD																															
COOPERATING UNITS (if any) Gwen Childs, Department of Anatomy, University of Texas Medical Branch, Galveston, Texas; Zvi Naor, Department of Hormone Research, Weizmann Institute of Science, Rehovot, Israel. Jack Vanderhoek, Department of Biochemistry, George Washington University, Washington, D.C.																																		
LAB/BRANCH Endocrinology and Reproduction Research Branch																																		
SECTION Section on Hormonal Regulation																																		
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205																																		
TOTAL MANYEARS: 5.0	PROFESSIONAL: 3.5	OTHER: 1.5																																
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																																		
SUMMARY OF WORK (200 words or less - underline keywords) The control of <u>pituitary hormone secretion</u> has been studied by analysis of <u>pituitary receptors</u> and/or responses to regulatory factors including <u>gonadotropin releasing hormone (GnRH)</u> , <u>angiotensin II (AII)</u> and <u>corticotropin releasing factor (CRF)</u> . In the rat, <u>pituitary GnRH receptors</u> were shown to be regulated directly by GnRH and its agonists, and to provide an index of endogenous GnRH secretion. GnRH receptors and actions were studied in <u>gonadotrophs purified from collagenase-dispersed pituitary cells by unit gravity sedimentation and centrifugal elutriation</u> , the latter method being of particular value for preparing fractions enriched in <u>lactotrophs and gonadotrophs</u> . <u>Synthetic GnRH agonists</u> were bound by <u>cultured gonadotrophs</u> in direct proportion to their biological potencies on <u>LH release</u> , and resistance to degradation was a minor factor at the <u>pituitary level</u> . <u>Up-regulation of receptors by GnRH agonists</u> was also demonstrated in <u>cultured pituitary cells</u> . <u>LH responses and desensitization to GnRH</u> were also analyzed in <u>perfused pituitary cells</u> , and further evidence for the role of <u>arachidonic acid metabolites in GnRH action</u> was obtained. Finally, <u>AII receptors</u> were identified in the anterior pituitary and localized to <u>lactotrophs</u> , which were shown to respond to AII with increased <u>prolactin secretion</u> .																																		

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00185-03 RR				
PERIOD COVERED October 1, 1981 - September 30, 1982						
TITLE OF PROJECT (80 characters or less) Effect of Temperature and Other Physical Factors on Localization, Natural History and Susceptibility to Disease.						
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width:100%; border: none;"> <tr> <td style="width:15%;">PI</td> <td style="width:35%;">D Rodbard</td> <td style="width:40%;">Head, Section on Biophysical Endocrinology</td> <td style="width:10%;">ERRB, NICHD</td> </tr> </table>			PI	D Rodbard	Head, Section on Biophysical Endocrinology	ERRB, NICHD
PI	D Rodbard	Head, Section on Biophysical Endocrinology	ERRB, NICHD			
COOPERATING UNITS (if any) Dept. of Medicine and Physical Medicine, Univ. of Sao Paulo, Brazil.						
LAB/BRANCH Endocrinology and Reproduction Research Branch						
SECTION Biophysical Endocrinology						
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205						
TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:				
CHECK APPROPRIATE BOX(ES)						
<input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER						
<input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS						
SUMMARY OF WORK (200 words or less - underline keywords)						
<p>The use of the thermographic camera has been examined in a variety of disease states. Thermography has been demonstrated to be useful in the detection and diagnosis of varicocele and testicular tumors. The thermographic camera is also useful in evaluation of temperature at the site of infectious disease (e.g. cutaneous and mucocutaneous leishmaniasis), and a variety of inflammatory diseases. Fever therapy or local heat therapy is being evaluated in a variety of disease states, including sporotrichosis, mucocutaneous leishmaniasis, and paracoccidioidomycosis.</p>						

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00187-03 RR															
PERIOD COVERED October 1, 1981 through September 30, 1982																	
TITLE OF PROJECT (80 characters or less) Hormonal Regulation of Cellular Metabolism																	
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width:100%; border: none;"> <tr> <td style="width:15%;">PI:</td> <td style="width:35%;">K.-P. Huang</td> <td style="width:30%;">Research Chemist</td> <td style="width:10%;">ERRB</td> <td style="width:10%;">NICHD</td> </tr> <tr> <td>OTHER:</td> <td>A. Akatsuka</td> <td>Visiting Fellow</td> <td>ERRB</td> <td>NICHD</td> </tr> <tr> <td></td> <td>T.J. Singh</td> <td>Visiting Fellow</td> <td>ERRB</td> <td>NICHD</td> </tr> </table>			PI:	K.-P. Huang	Research Chemist	ERRB	NICHD	OTHER:	A. Akatsuka	Visiting Fellow	ERRB	NICHD		T.J. Singh	Visiting Fellow	ERRB	NICHD
PI:	K.-P. Huang	Research Chemist	ERRB	NICHD													
OTHER:	A. Akatsuka	Visiting Fellow	ERRB	NICHD													
	T.J. Singh	Visiting Fellow	ERRB	NICHD													
COOPERATING UNITS (if any) J. Chou, PRB, NICHD; P.B. Chock, LB, NHLBI																	
LAB/BRANCH Endocrinology and Reproduction Research Branch																	
SECTION																	
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, MD 20205																	
TOTAL MANYEARS: 3.0	PROFESSIONAL: 3.0	OTHER: 0.0															
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																	
SUMMARY OF WORK (200 words or less - underline keywords) <p> <u>Phosphorylation and dephosphorylation</u> of the enzymes controlling the <u>rate-limiting step</u> is a most important <u>regulatory mechanism</u> for cellular <u>metabolism</u>. In <u>diabetic animals</u> the regulation of <u>glycogen metabolism</u> by this regulatory mechanism becomes defective and the defect can be corrected by the administration of <u>insulin</u>. The purposes of this work are: (1) to study the regulation of <u>glycogen synthase</u> and <u>phosphorylase kinase</u> activities by <u>protein kinases</u> and <u>phosphoprotein phosphatases</u>; (2) to define the defect in <u>glycogen metabolism</u> resulting from diabetes; and (3) to elucidate the mechanism of action of insulin. </p>																	

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01HD00188-02 RR.
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PERIOD COVERED
October 1, 1981 - September 30, 1982.

TITLE OF PROJECT (80 characters or less)
Development of new analogs of Enkephalin with increased receptor activity and selectivity.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI	D. Rodbard	Head, Section on Biophysical Endocrinology	ERRB, NICHD
	S. Krumins	Visiting Fellow	ERRB, NICHD
	Y. Shimohigashi	Visiting Fellow	ERRB, NICHD
	H. Chen	Senior Investigator	ERRB, NICHD

COOPERATING UNITS (if any)
Yerkes Primate Center, Atlanta Georgia.
Max-Plank Institute for Psychiatry, Munich, Germany, Laboratory of Biochemistry, National Institute of Mental Health.

LAB/BRANCH
Endocrinology and Reproduction Research Branch

SECTION
Biophysical Endocrinology Section

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2	PROFESSIONAL: 2	OTHER:
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Several series of new dimeric analogs of enkephalin penta-, tetra- and tri-peptides have been synthesized, purified, and characterized by several physical chemical techniques, binding assays, bioassays, and in vitro bioassays. The new analogs show extremely high potency and specificity for the "delta" opiate receptor, and are useful in the characterization of opiate receptors, autoradiographic and pharmacological applications. Binding kinetics are compatible with the hypothesis that the ligands bind simultaneously to two receptors. Effects of ions (Mn^{2+} , Na^+) and GTP on binding of monomers and dimer have been compared. The ability of the dimers to induce desensitization and tolerance in NG108-15 cells has been characterized, and appears to differ qualitatively from that of the monomers. Additional new compounds include alkyl-enkephalin amides and a mono-N-acetyl enkephalin. The latter compound provides a novel probe of the delta receptor.

PERIOD COVERED

October 1, 1981 - September 30, 1982

TITLE OF PROJECT (100 characters or less)

Development of Statistical software for use by clinical and laboratory investigators.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI	D. Rodbard	Head, Section on Biophysical Endocrinology	ERRB, NICHD
	P. J. Munson	Mathematician-Statistician	ERRB, NICHD
Other	B. Cole	Systems Analyst	DMB, DCRT
	A. Faust		CC
	T. Lewis		CC
	J. Cinino	Medical Student	
	J. English	Medical Student	
	E. Wong	Medical Student	

COOPERATING UNITS (if any)

LAB/BRANCH

Endocrinology and Reproduction Research Branch

SECTION

Biophysical Endocrinology

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:

1

PROFESSIONAL:

1

OTHER:

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

We are attempting to develop new and improved techniques of statistical computing for use by clinical and laboratory investigators throughout NICHD and NIH. This software is intended for persons with no previous computer experience and only modest background in biostatistics. The system is easy to learn, easy to use, and virtually self-teaching. Its hallmarks are the automatic testing of underlying assumptions, provision of warnings when assumptions are violated; a verbal interpretation of results, and suggestion of other appropriate techniques. Improved computer graphics are provided for retrospective review of laboratory data on current in-patients, out-patients, as well as for archival data.

DEVELOPMENTAL ENDOCRINOLOGY BRANCH

ANNUAL REPORT

October 1, 1981 - September 30, 1982

<u>Project #</u>	<u>Project Title</u>	<u>Principle Investigator</u>
Z01 HD 00610-02	Physiology of Puberty.....	G. Cutler, Jr., M.D.
Z01 HD 00611-02	Pathophysiology of Gynecomastia and Hirsutism.....	D.L. Loriaux, M.D.
Z01 HD 00612-02	Role of Sex Steroids in Regulation of FSH and LH Levels in Man.....	R.J. Sherins, M.D.
Z01 HD 00613-02	Clinical Studies of Male Reproductive Disorders.....	R.J. Sherins, M.D.
Z01 HD 00614-02	Biology of Hormone Binding Proteins.....	B.C. Nisula, M.D.
Z01 HD 00615-02	Steroid Antagonists.....	G. Cutler, Jr., M.D.
Z01 HD 00616-02	Structure, Function, and Physiology of Glycoprotein Hormones.....	B.C. Nisula, M.D.
Z01 HD 00617-02	Catechol Estrogens: Physiological Effects.....	D.L. Loriaux, M.D.
Z01 HD 00618-01	Physiology and Clinical Application of Corticotropin Releasing Hormone....	G.B. Chrousos, M.D.
Z01 HD 00619-01	Hypothalamic-Pituitary-Gonadal Interaction.....	D.L. Loriaux, M.D.
Z01 HD 00620-01	Steroid and Peptide Hormone Action...	D.L. Loriaux, M.D.

ANNUAL REPORT
Summary

DEVELOPMENTAL ENDOCRINOLOGY BRANCH
National Institute of Child Health and Human Development

The research aim of the Developmental Endocrinology Branch is to further our understanding of the role of the endocrine system in the complex process of growth and development. The periods of primary interest include fetal and neonatal life, puberty, and senility. The current focus of research is the pubertal period. The systems under study are two; the hypothalamic-pituitary-gonadal axis and the hypothalamic-pituitary-adrenal axis.

Studies on the hypothalamic-pituitary-gonadal axis are directed toward understanding the initiation of LH and FSH secretion which heralds the onset of puberty, the mechanism of action of these glycoprotein hormones, the gonadal response to these hormones, and the roles of the gonadal sex steroids in gametogenesis, central nervous system maturation, breast physiology, hair growth, and skeletal maturation.

Specific areas of investigation include the temporal patterns of GNRH and gonadotropin secretion, the mechanism of the pubertal growth spurt, the treatment of idiopathic true precocious puberty with an analog of luteinizing hormone releasing hormone, the development and use of luteinizing hormone releasing hormone agonists that can be administered intranasally, examining the normal patterns of LHRH-LH-FSH release during childhood, puberty, and during the normal menstrual cycle, and the interactions between the theca and granulosa cell compartments of the ovary and how this interfaces with pituitary function. Also under study are the effects of gonadal steroids in regulating LH & FSH secretion. An examination of the hypothesis that a non-steroidal molecule of gonadal origin is important in FSH regulation is also underway. The structure-function relationships between the glycoprotein hormones, FSH, LH, hCG & TSH, is also an important area of research. Relationships under study include structure-activity relationships of glycoprotein hormone binding to membrane receptor sites, patterns of metabolic disposal and comparisons between degradation products of the various glycoprotein hormones.

Studies on the actions of gonadal hormones include experiments designed to elucidate the origin, disposition, and metabolic effects of the catechol estrogens. Also under study are the pathophysiologic mechanisms of disordered secondary sexual phenotypic expression, including such disorders as gynecomastia and hirsutism. The role of the circulating plasma sex steroid binding proteins, CBG & SHBG in modulating steroid hormone action are also being examined in these studies.

Several other clinically important disorders of the hypothalamic-pituitary-gonadal axis are currently under study. These include male and female hypogonadotropic hypogonadism and the syndrome of hyperprolactinemia, amenorrhea & galactorrhea. The natural history of these conditions as well as new forms of therapeutic intervention are being evaluated.

Studies on the hypothalamic-pituitary-adrenal axis include investigations into the physiology of adrenarche in man and the chimpanzee, the only known

animal model for this process. Studies on the fetal adrenal zone are also in progress. These studies employ the marmoset as an experimental model. The role of corticotropin releasing hormone (CRH) in normal physiology and in disorders of pituitary-adrenal function is being studied. Rapid progress in this area has been made possible by the recent discovery of the chemical structure of CRH. Our objectives are to determine the dose-response relationship for CRH in primates and man, to study the metabolic clearance rate of CRH in these species, to develop methods to measure CRH accurately in tissue and biological fluids, and to evaluate the potential utility of this compound in the diagnosis and treatment of adrenal insufficiency and Cushing's disease. Also under development are methods to measure CRH receptors that will allow the exploration of the role of receptor regulation as a modulator of tissue sensitivity to CRH.

Finally, we hope to understand the physiologic actions of the various steroid and peptide hormones of the pituitary-adrenal axis and how these effects are mediated. Of current interest are the stress modulating effects of glucocorticoid hormones and the endogenous opiate peptides. To this end, we are studying several clinical examples of disordered hypothalamic-pituitary-adrenal function including ACTH dependent Cushing's Syndrome, adrenal cancer, congenital adrenal hyperplasia, adrenal insufficiency, and endogenous depression. We are also studying two models of glucocorticoid hormone resistance; glucocorticoid resistance in New World primates, and glucocorticoid resistance in a family of Dutch descent. Both of these forms of glucocorticoid resistance have been found to be due to defective glucocorticoid receptors. Continued study of these examples of hormone resistance promises to enhance our understanding of the mechanism steroid hormone action.

PERIOD COVERED
October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)

Physiology of Puberty

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G.B. Cutler, Jr., M.D., Senior Investigator	DEB, NICHD, NIH
Other:	D.L. Loriaux, M.D., Ph.D., Chief	DEB, NICHD, NIH
	B. Albertson, Ph.D., Staff Fellow	DEB, NICHD, NIH
	J. Booth, M.D., Visiting Associate	DEB, NICHD, NIH
	F. Cassorla, M.D., Med. Staff Fellow	DEB, NICHD, NIH
	G. Chrousos, M.D., Visiting Scientist	Clin Ctr, NIH
	F. Comite, M.D., Med. Staff Fellow	DEB, NICHD, NIH
	C. Foster, M.D., Med. Staff Fellow	DPB, NICHD, NIH
	K. Hench, R.N.	9West, Clin Ctr, NIH
	J. Levine, M.D., Med. Staff Fellow	DEB, NICHD, NIH
	A. McNemar, R.N.	9West, Clin Ctr, NIH
	M. Skerda, R.N.	9West, Clin Ctr, NIH
	W. Sonis, M.D., Med. Staff Fellow	SBS, NICHD, NIH
	J. Winterer, M.D., Ph.D., Med. Staff Fellow	DEB, NICHD, NIH

COOPERATING UNITS (if any)

E. Susman, Ph.D.	LDP, NIMH
G. Inoff, Ph.D.	LDP, NIMH

LAB/BRANCH

Developmental Endocrinology Branch

SECTION

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:

8

PROFESSIONAL:

7

OTHER:

1

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to gain insight into the physiologic processes underlying normal and abnormal pubertal progression. Principal areas of investigation include the mechanisms of adrenarche, the temporal changes in hypothalamic function with respect to gonadotropin regulation, the mechanism of the pubertal growth spurt, the treatment of idiopathic true precocious puberty with an analog of luteinizing hormone releasing hormone, and the development and use of luteinizing hormone releasing hormone agonists that can be administered by an intranasal route.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00611-2 DEB
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PERIOD COVERED
October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)
Pathophysiology of Gynecomastia and Hirsutism

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.L. Loriaux, M.D., Ph.D., Chief	DEB/NICHD
Other:	J. Booth, M.D., Guest Worker	DEB/NICHD
	S. Brody, M.D., Clinical Associate	DEB/NICHD
	G. Chrousos, M.D., Clinical Associate	DEB/NICHD
	G. Cutler, M.D., Senior Investigator	DEB/NICHD
	M. Koppelman, M.D., Clinical Associate	DEB/NICHD
	G. Merriam, M.D., Clinical Associate	DEB/NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Developmental Endocrinology Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2	PROFESSIONAL: 2	OTHER:
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to understand the pathophysiology of disordered secondary sexual phenotypic expression, including such disorders as gynecomastia and hirsutism. Progress in the last year has centered around the investigation of an outbreak of gynecomastia in Hatian refugees, isolating the pathophysiologic agent, and in completing a study on the natural history of the syndrome of amenorrhea and galactorrhea and assessing the role of prolactin in altering hypothalamic-pituitary-gonadal function in these women.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00612-02 DEB
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PERIOD COVERED
October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)
Role of Sex Steroids in Regulation of FSH and LH Levels in Man

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.J. Sherins, M.D., Senior Investigator	DEB, NICHD, NIH
Other:	D.L. Loriaux, M.D., Ph.D., Chief	DEB, NICHD, NIH
	B.C. Nisula, M.D., Senior Investigator	DEB, NICHD, NIH
	J. Booth, M.D., Visiting Scientist	DEB, NICHD, NIH
	G.R. Merriam, M.D., Clinical Associate	DEB, NICHD, NIH
	S. Brody, M.D., Clinical Associate	DEB, NICHD, NIH
	J. Winterer, M.D., Clinical Associate	DEB, NICHD, NIH
	R.V. Clark, M.D., Clinical Associate	DEB, NICHD, NIH
	YF Shi, M.D., Visiting Associate	DEB, NICHD, NIH
	D. Vogel, M.D., Clinical Associate	DEB, NICHD, NIH
	A. Patterson, Student	DEB, NICHD, NIH

COOPERATING UNITS (if any)

LAB/BRANCH
Developmental Endocrinology Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 4	PROFESSIONAL: 2	OTHER: 2
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A series of studies in the rat have been utilized to ascertain the extent to which testosterone and estradiol can regulate the secretion of FSH and LH in the absence of the testes. The data demonstrate that 1) testosterone alone at physiologic doses can maintain both gonadotropins within the normal range, 2) that estradiol alone preferentially suppresses LH, but not FSH concentrations and 3) that a selective increase in plasma FSH is produced when there is reduced androgen production in association with increased estradiol production. Similar changes are seen in the pituitary content of FSH and LH suggesting that these altered sex steroid levels effect gonadotropin synthesis, storage and release. These data provide an alternate explanation for the inhibin hypothesis which suggests that there is a specific non sex steroid inhibitor of FSH secretion arising from the seminiferous tubules.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 HD 00613-02 DEB

PERIOD COVERED

October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)

Clinical Studies of Male Reproductive Disorders

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R.J. Sherins, M.D., Senior Investigator DEB, NICHD, NIH

Other: R.V. Clark, M.D., Clinical Associate DEB, NICHD, NIH
T. Kinsella, M.D., Senior Investigator NCI, NIH
S. Rosenberg, M.D., Senior Investigator NCI, NIH

COOPERATING UNITS (if any)

C. Wayne Bardin, M.D., Director, Population Council Rockefeller University,
New York
Claude Gagnon, Ph.D., Laval University, Quebec, CANADA

LAB/BRANCH

Developmental Endocrinology Branch

SECTION

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:

5.0

PROFESSIONAL:

4.0

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS

(b) HUMAN TISSUES

(c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A variety of studies of clinical disorders of male reproduction are in progress. These include 1) studies of the hormonal regulation of spermatogenesis in hypogonadotropic men, 2) analysis of biochemical parameters of sperm metabolism in men with non-motile sperm, 3) longitudinal evaluation of the adverse effects of cytotoxic drugs on testicular function in men receiving chemotherapy for malignant disorders, and 4) the evaluation of treatment of men with idiopathic infertility.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 HD 00614-02 DEB

PERIOD COVERED
October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)
Biology of Hormone Binding Proteins

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: B.C. Nisula, M.D., Senior Investigator DEB, NICHD, NIH

Other: R. Clark, M.D., Med. Staff Fellow DEB, NICHD, NIH
R.J. Sherins, M.D., Senior Investigator DEB, NICHD, NIH
D.L. Loriaux, M.D., Ph.D., Chief DEB, NICHD, NIH

COOPERATING UNITS (if any)

LAB/BRANCH
Developmental Endocrinology Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINDRS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)
The broad objective of this project is to understand the biology of the serum hormone binding proteins and the role that they play in various human disease states. Recent research findings include the following: development of a new approach for assessment of the significance of drug interactions with human steroid binding proteins; elucidation of evidence that idiopathic hirsutism is due to excessive androgen secretion of both adrenal and ovarian etiology; and demonstration that testosterone-binding globulin levels are normal in patients with familial thyroid hormone resistance while markedly elevated in thyrotoxicosis. Future directions of the project will emphasize delineating the role of steroid binding proteins (corticosteroid-binding globulin and testosterone-binding globulin) in hormonal action in various tissues and elucidating pharmacological and pathological factors modulating the levels of the binding globulins.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00615-02 DEB
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PERIOD COVERED
October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)
Steroid Antagonists

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G.B. Cutler, Jr., M.D., Sr. Investigator	DEB, NICHD, NIH
Other:	D. Lynn Loriaux, M.D., Ph.D., Chief	DEB, NICHD, NIH
	G. Chrousos, M.D., Visiting Scientist	Clin. Ctr, NIH
	M.A. Sauer, Chemist	DEB, NICHD, NIH

COOPERATING UNITS (if any)
Marvin Karten

LAB/BRANCH
Developmental Endocrinology Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2	PROFESSIONAL: 1	OTHER: 1
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Clinically useful antagonists exist for estrogens, androgens, and mineralocorticoids. No antagonists have been identified for the glucocorticoids or the progestins. The objective of this project is to develop antagonists for both of these classes of steroids.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 HD 00616-02 DEB

PERIOD COVERED

October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)

Structure, Function, and Physiology of Glycoprotein Hormones

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	B. Nisula, M.D., Senior Investigator	DEB, NICHD, NIH
Other:	S. Amr, M.D., Visiting Fellow	DEB, NICHD, NIH
	D. Bliethe, Ph.D., Staff Fellow	DEB, NICHD, NIH
	G. Lefort, M.D., Visiting Fellow	DEB, NICHD, NIH

COOPERATING UNITS (if any)

LAB/BRANCH

Developmental Endocrinology Branch

SECTION

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:

3.0

PROFESSIONAL:

3.0

OTHER:

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The general goal of this project is to understand the structure, function, and physiology of the glycoprotein hormones-thyrotropin, chorionic gonadotropin, luteinizing hormone and follicle-stimulating hormone--and to elucidate the role of glycoprotein hormone derangements in human diseases. Recent research findings include the following: demonstration of the clinical value of a highly sensitive urinary chorionic gonadotropin assay in the management of patients with gestational trophoblastic neoplasia; characterization of the heterogeneous nature of chorionic gonadotropin preparations used by physicians in hypogonadotropic patients; and elucidation of a role for prostaglandins in mediating an immunosuppressive effect of chorionic gonadotropin. Future emphasis of the project will be on structure-activity relationships of glycoprotein hormone binding sites in thyroid membranes, metabolic disposal and degradation products of glycoproteins, and the clinical relevance of hormonal heterogeneity.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00617-2 DEB															
PERIOD COVERED October 1, 1981 - September 30, 1982																	
TITLE OF PROJECT (80 characters or less) Catechol Estrogens: Physiological Effects																	
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0"> <tr> <td>PI:</td> <td>D.L. Loriaux, M.D., Ph.D., Chief</td> <td>DEB/NICHD</td> </tr> <tr> <td>Other:</td> <td>D.D. Brandon, Chemist</td> <td>Clin Ctr/NICHD</td> </tr> <tr> <td></td> <td>M.B. Lipsett, M.D., Director</td> <td>NICHD</td> </tr> <tr> <td></td> <td>G.R. Merriam, M.D., Clinical Associate</td> <td>DEB/NICHD</td> </tr> <tr> <td></td> <td>D. Pfieffer, M.D., Visiting Associate</td> <td>DEB/NICHD</td> </tr> </table>			PI:	D.L. Loriaux, M.D., Ph.D., Chief	DEB/NICHD	Other:	D.D. Brandon, Chemist	Clin Ctr/NICHD		M.B. Lipsett, M.D., Director	NICHD		G.R. Merriam, M.D., Clinical Associate	DEB/NICHD		D. Pfieffer, M.D., Visiting Associate	DEB/NICHD
PI:	D.L. Loriaux, M.D., Ph.D., Chief	DEB/NICHD															
Other:	D.D. Brandon, Chemist	Clin Ctr/NICHD															
	M.B. Lipsett, M.D., Director	NICHD															
	G.R. Merriam, M.D., Clinical Associate	DEB/NICHD															
	D. Pfieffer, M.D., Visiting Associate	DEB/NICHD															
COOPERATING UNITS (if any)																	
LAB/BRANCH Developmental Endocrinology Branch																	
SECTION																	
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205																	
TOTAL MANYEARS: 2	PROFESSIONAL: 2	OTHER:															
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																	
SUMMARY OF WORK (200 words or less - underline keywords) The <u>catechol estrogens</u> , 2 or 4 hydroxyderivatives of estrone and estradiol, represent major metabolites of the naturally occurring estrogens. Little is known about the <u>origin, disposition, and metabolic effects</u> of these compounds. The objective of this project is to answer these questions. Progress to date reveals the catechol estrogens to be weak estrogen agonists, the 4-hydroxy compounds being stronger than the 2 hydroxy isomers, with no evidence of estrogen antagonist activity. The metabolic clearance of these compounds is extremely rapid, more than 20,000 L/day, and they appear to serve primarily as deactivated metabolites of estrone and estradiol.																	

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 HD 00618-01 DEB

PERIOD COVERED

October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)

Physiology and Clinical Application of Corticotropin Releasing Hormone

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G.B. Chrousos, M.D., Visiting Scientist	Clinical Ctr/NIH
Other:	G.B. Cutler, Jr., M.D., Senior Investigator	DEB/NICHD/NIH
	P. Gold, M.D., Senior Investigator	LCS/ NIMH/ NIH
	D.L. Loriaux, M.D., Ph.D., Chief	DEB/NICHD/NIH
	E. Oldfield, M.D., Medical Staff Fellow	SNB/NINCDS/NIH
	H. Schulte, M.D., Visiting Associate	DEB/NICHD/NIH

COOPERATING UNITS (if any)

LAB/BRANCH

Developmental Endocrinology Branch

SECTION

INSTITUTE AND LOCATION

NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:

4

PROFESSIONAL:

4

OTHER:

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS

(b) HUMAN TISSUES

(c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

We seek in this project to advance understanding of the role of corticotropin releasing hormone (CRH) in normal physiology and in disorders of pituitary-adrenal function. Rapid progress in this area has been made possible by the recent discovery of the chemical structure of CRH. Our objectives are to determine the dose-response relationship for CRH in primates and in humans, to study the metabolic clearance rate of CRH in primates and in man, to develop methods to measure CRH accurately in tissue and in biological fluids, to measure CRH in the plasma and cerebrospinal fluid of patients with Cushing's disease, to develop a clinical CRH test and to evaluate its usefulness in adrenal insufficiency and Cushing's disease, and to develop methods to measure CRH receptors so that we can explore the role of receptor regulation as a modulator of tissue sensitivity to CRH.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00619-01 DEB																		
PERIOD COVERED October 1, 1981 - September 30, 1982																				
TITLE OF PROJECT (80 characters or less) Hypothalamic-Pituitary-Gonadal Interaction																				
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table border="0" style="width: 100%;"> <tr> <td style="width: 10%;">PI:</td> <td style="width: 70%;">D.L. Loriaux, M.D., Ph.D., Chief</td> <td style="width: 20%;">DEB/NICHD</td> </tr> <tr> <td>Other:</td> <td>B.D. Albertson, Ph.D., Staff Fellow</td> <td>DEB/NICHD</td> </tr> <tr> <td></td> <td>S. Brody, M.D., Clinical Associate</td> <td>DEB/NICHD</td> </tr> <tr> <td></td> <td>F. Cassorla, M.D., Clinical Associate</td> <td>DEB/NICHD</td> </tr> <tr> <td></td> <td>G. Merriam, M.D., Clinical Associate</td> <td>DEB/NICHD</td> </tr> <tr> <td></td> <td>A. Munabi, M.D., Clinical Associate</td> <td>DEB/NICHD</td> </tr> </table>			PI:	D.L. Loriaux, M.D., Ph.D., Chief	DEB/NICHD	Other:	B.D. Albertson, Ph.D., Staff Fellow	DEB/NICHD		S. Brody, M.D., Clinical Associate	DEB/NICHD		F. Cassorla, M.D., Clinical Associate	DEB/NICHD		G. Merriam, M.D., Clinical Associate	DEB/NICHD		A. Munabi, M.D., Clinical Associate	DEB/NICHD
PI:	D.L. Loriaux, M.D., Ph.D., Chief	DEB/NICHD																		
Other:	B.D. Albertson, Ph.D., Staff Fellow	DEB/NICHD																		
	S. Brody, M.D., Clinical Associate	DEB/NICHD																		
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	G. Merriam, M.D., Clinical Associate	DEB/NICHD																		
	A. Munabi, M.D., Clinical Associate	DEB/NICHD																		
COOPERATING UNITS (if any)																				
LAB/BRANCH Developmental Endocrinology Branch																				
SECTION																				
INSTITUTE AND LOCATION NICHD, NIH, Bethesda, Maryland 20205																				
TOTAL MANYEARS: 2	PROFESSIONAL: 2	OTHER:																		
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																				
SUMMARY OF WORK (200 words or less - underline keywords) The objective of this study is to understand the basic <u>physiology of hypo-</u> <u>thalamic-pituitary-gonadal interaction</u> . The focus of our current studies is the interaction between the hypothalamus and pituitary gland, examining the <u>normal patterns of LHRH-LH-FSH release during the normal menstrual cycle,</u> <u>and on the interactions between the theca and granulosa cell compartments</u> of the ovary and how this interfaces with pituitary function.																				

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 HD 00620-1 DEB
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PERIOD COVERED
October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)
Steroid and Peptide Hormone Action

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.L. Loriaux, M.D., Ph.D., Chief	DEB/NICHD
Other:	D.D. Brandon, Chemist	Clin Ctr/NICHD
	G.C. Chrousos, M.D.	Clin Ctr/NICHD
	M.C. Koppelman, M.D., Clinical Associate	DEB/NICHD
	M.B. Lipsett, M.D., Director	NICHD
	R.G. Rittmaster, M.D., Clinical Associate	DEB/NICHD

COOPERATING UNITS (if any)

LAB/BRANCH
Developmental Endocrinology Branch

SECTION

INSTITUTE AND LOCATION
NICHD, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2	PROFESSIONAL: 2	OTHER:
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CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER

(a1) MINORS (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The broad objective of the project is to understand what the actions of the various steroid and peptide (LH, FSH, prolactin) hormones are and how these effects are mediated. Currently under study are two models of steroid hormone resistance; glucocorticoid resistance in the New World primates, and glucocorticoid resistance in man. Both of these forms of glucocorticoid resistance have been found to be due to defective glucocorticoid receptors.

Also under study are the extramammary actions of prolactin. In particular, the effect of prolactin on hypothalamic-pituitary-gonadal function is currently under investigation.

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