

laboratory, Chemistry and Chemical Biology, a few months ago. Cerione's laboratory uses molecular biology to prepare mutant forms of transglutaminase that, when considered in combination with the three-dimensional structure, should lead to a fuller understanding of transglutaminase and its potential as a target for cancer therapy.

Cancer research of the sort described here requires a synthesis of genetic understanding of mutations, pathway analysis, three-dimensional structure determination, and chemical synthesis. Cornell is fortunate to have strengths in all of these areas.



Biomedical Research in the Division  
of Nutritional Sciences Probes  
Links Between Maternal and Child  
Nutrition and Lifelong Health

DNS has been a leader in human nutrition research, in part, because it approaches human health from a multidisciplinary perspective. Surrounding a core of scientists trained in the traditional discipline of nutrition are faculty who represent such diverse basic science disciplines as biochemistry, molecular and cell biology, and physical chemistry as well as translational and applied disciplines such as toxicology, public health, epidemiology, psychology, sociology, anthropology, and economics. Integration of methods and theories from these disciplines has allowed DNS to investigate the whole person within the context of the family, community, and society into which the individual is born, raised, and functions through adulthood and into old age. Thus, a major approach to nutrition is through a life course perspective that recognizes the importance of genetic endowment and its varied expression in the individual depending on the environment encountered from conception to death. Nutrition is an indispensable component of that environment which is known to affect the way genes are expressed. It is in this context that the science of nutrition is expected to make important contributions to biomedical and public health research.

One area of research that involves a large number of DNS faculty relates to the nutrition problems surrounding pregnancy and early infancy. Research in maternal and child nutrition has implications for both the United States and developing countries, and DNS researchers are active in both arenas. This research bridges the basic and applied sciences in DNS. Recent laboratory research in the Division of Nutritional Sciences has contributed to new knowledge about the mechanisms of genetic control of nutrient metabolism associated with fetal malformation, the contribution of

**“It is increasingly recognized that many diseases afflicting the U.S. population are preventable with changes in lifestyle. These include heart disease, cancer, and diabetes—the top three killers of Americans.”**

fatty acids to fetal brain development, and the lasting effects of prenatal cocaine exposure on cognitive functioning. The translation of nutrition laboratory research to the improvement of diets and nutritional status of population groups is seen in epidemiologic research on such issues as: the risks of becoming obese following childbirth, the impact of maternal obesity on breast feeding, the impact of federal nutrition programs on reducing health risks among the poorest of Americans, and the development of new reference charts to assess child growth worldwide.

The research highlighted here deals with nutrition issues affecting mothers and infants, widely considered as the most nutritionally vulnerable groups. While nutrition exerts a strong and immediate impact on the mother and infant at the time of pregnancy and for the first few postnatal years, there is mounting evidence that the long-term impact of the early nutrition experience may be instrumental to understanding lifelong human development and the onset of disease in adulthood. This sampling of research on human nutrition in the DNS, however, represents the importance of studying nutrition from a variety of scientific approaches and at different levels of biological organization—from molecules to the population.

## Laboratory-Based Research

Recent advances in mapping the human genome have important implications for human nutrition. The Cornell Institute for Nutritional Genomics (CING) was created to coordinate much of this effort on the Cornell campus. Among the CING research programs is one that examines the contribution of folic acid to prenatal development. Patrick Stover studies folate metabolism, a process that is critical to cell growth and therefore important to developing fetuses. Deficiencies of folic acid in the maternal diet are known to contribute to malformations of the spinal cord and brain. These neural tube defects include spina bifida—a condition in which part of the spinal cord remains outside the body—and anencephaly—a condition in which the skull and brain fail to form completely. Cellular folate levels are also connected to the initiation and subsequent growth of cancerous tumors and to the development of heart disease. Stover’s laboratory

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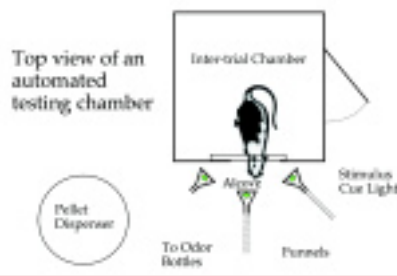


“ Cutberto Garza studies nutrition during the fetal life and early infancy with special interest in the “imprinting” of metabolic responses and how it relates to cardiovascular health and to insulin metabolism.

Barbara Strupp studies the ► consequences of poor prenatal environment on cognitive development in the newborn, particularly the effects of cocaine use during pregnancy.



Robert Barker/CU



In both the lead and cocaine projects, the animals receive a series of cognitive tasks designed to test a broad range of cognitive functions, analogous to a human neuropsychological testing battery. These tasks are administered

in automated testing chambers, each controlled by a PC. A correct response is rewarded with a small piece of food. The complete test battery requires 2 to 3 months of daily testing per animal.

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identifies and clones human and mouse genes that code for several key folate-dependent enzymes. These enzymes regulate folate status and metabolism during development. Stover's group uses molecular-genetic techniques to create stable human cell-culture lines and to create transgenic mice with altered expression of the genes. This enables the researchers to characterize the factors responsible for the expression of these genes and to define the roles of the gene products in development and disease processes.

The body's requirements for fatty acids during early life is the research interest of J. Thomas Brenna, who investigates the role of omega-3 fatty acids in fetal and newborn brain and associated organ development. Polyunsaturated fatty acids are involved in a variety of physiological processes. They are particularly critical in the perinatal period when the developing fetus or newborn is forming neural tissue with membranes rich in unsaturated fatty acids. The predominant long chain polyunsaturated (LCP) fatty acids, arachidonic and docosahexaenoic acids, are present in high concentration in the brain cortex and in particular phospholipids of the retinal photoreceptor cells. Since mammals cannot synthesize omega-3 or omega-6 fatty acids de novo, their nutritional supply during development is critical. Healthy infants can consume adequate amounts of all long chain polyunsaturates and unsaturated fatty acids from breast milk, but there is much controversy as to whether conventional formulas devoid of LCP meet the needs of formula-fed infants. Of even more concern is the nutrition of premature infants, most of whom now survive after gestational periods of less than 30 weeks and with birth weights of less than 600 grams. Their nutritional requirements are ill defined because their survival rates were very low until the advances in neonatal medicine of the last two decades; thus, neither breast milk nor traditional formula can be assumed to meet their needs.

In collaboration with colleagues in Cornell's College of Veterinary Medicine, Brenna's research group administers tracer doses of essential fatty acids to pregnant primates and analyzes fetal tissues to determine levels of accumulation and metabolism. This work has shown that large amounts of essential fatty acids are metabolized in pathways other than those required for essential components of neural tissue, indicating that the role of the fatty acids is

more complex and even more critical than previously supposed. The group has also established the relative efficacy of linolenic acid as a precursor to the structurally important docosahexaenoic acid in pregnancy and in neonatal baboons.

Nutrition during fetal life and early infancy is also the interest of Cutberto Garza. His research is motivated by increasing evidence that nutritional events during this time of life and nutritional conditions that prevail also at later times “imprint” specific metabolic responses. These responses appear to help determine individual risk to short- and long-term outcomes of cardiovascular health and the functioning of insulin metabolism. The potential relevance of metabolic imprinting is evident in the physiologic differences between breast- and bottle-fed infants that Garza and his colleagues studied and, more recently, in the epidemiologic data that link birth weight to the risk of several chronic diseases of adulthood. Garza's laboratory studies the basic biological mechanisms that account for imprinting.

Barbara Strupp studies the consequences of poor prenatal environment on cognitive development in the newborn. She uses experimental animals to investigate the effects of cocaine exposure during pregnancy. Researchers are becoming increasingly concerned about the effects of cocaine use during pregnancy because of the growing incidence of cocaine-exposed babies. Yet, researchers find it difficult to isolate the specific effects of prenatal exposure to the drug in children because of confounding factors such as prenatal undernutrition, maternal stress, prenatal care, and quality of the postnatal environment and accompanying exposure to alcohol, nicotine, marijuana, opiates, and amphetamines. Strupp's research, conducted in collaboration with scientists at the University of Kentucky, involved the surgical implantation of catheters into pregnant rats—half received doses of cocaine comparable to human “recreational doses” and half received a harmless saline solution. Offspring then went through a series of cognitive tasks. The researchers found that prenatal cocaine produced its most significant effect on selective attention in rats—the ability to stay focused despite environmental distractions. This research suggests a connection between cocaine use during pregnancy and attention dysfunction in children.

Strupp's lab also studies an animal model of lead exposure during infancy and early childhood. As in the case of prenatal cocaine exposure, childhood lead exposure disproportionately affects children in poverty, making it difficult to determine whether the IQ deficits seen in lead-exposed children are due to lead exposure or to the risk factors associated with growing up in poverty. These numerous risk factors complicate the identification of the specific cognitive or affective functions that are affected by early lead exposure. Strupp's research has shown that exposure to lead during the lactational period

Sheryl Sinkow/CU



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Christine Olson (l.) and Kathleen Rasmussen (r.) each study different topics on the effects of weight gain during pregnancy on the long-term health of the mother.

(exposure via breast milk) can produce lasting deficits in learning ability and the ability to sustain attention. Recent studies have shown that previously lead exposed rats are more adversely affected by their errors than controls, with the consequence of additional errors more likely. Ongoing studies are designed to determine whether this heightened reaction to errors indicates a general problem with the regulation of emotions. These deficits in learning ability and attention, coupled with increased error reactivity, are likely to contribute significantly to the IQ deficits and delinquency associated with lead exposure in children. Ongoing studies examine the neural bases of these cognitive and affective deficits, as well as testing whether these deficits can be prevented or ameliorated by the administration of a new chelating agent, Succimer. Succimer appears to have many benefits over currently used chelating agents, leading to hopes of significant therapeutic potential.

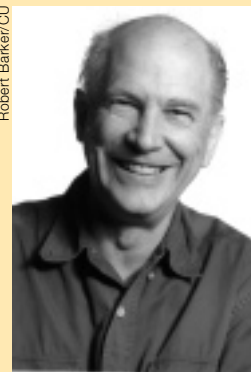
## Population-Based Research

Obesity is an important public health nutrition problem in the United States. More than one-half of American adult women are overweight and nearly half of these women could be classified as obese. The problem of obesity in women often emerges during pregnancy and the immediate postpartum period. In the past, the amount of weight a woman gained during pregnancy was evaluated relative to its effect on growth of the fetus, in order to achieve an optimum birth weight. Little regard was given to the consequences of weight gained during pregnancy and its effect on the long-term health of the mother, nor on her capacity to breast-feed her newborn infant. Christine Olson and Kathleen Rasmussen are investigating different aspects of this problem.

In collaboration with researchers from the Research Institute of Bassett Healthcare in Cooperstown, New York, Olson's research group found that more than 40 percent of 577 rural women surveyed gained more weight during pregnancy than is recommended by the Institute of Medicine of the National Academy of Sciences. Furthermore, one-fourth of all the pregnant women studied were at least 10 pounds heavier one year after giving birth. Olson found that women in the study gained an average of almost four pounds by the end of the first year following a pregnancy. Of particular importance is the observation that 56 percent of the new cases of obesity in this study could have been prevented if the women had stayed within the recommended ranges for weight gain during pregnancy. Olson is continuing this study by including a multiethnic urban population in collaboration with scientists from the University of Rochester Medical School.

Rasmussen investigates, with colleagues at Bassett Healthcare, the effects of maternal obesity on lactation performance. Findings from their latest study of 2,494 single births show that normal-weight women who gain more than 24 to 35 pounds during pregnancy (recommended by the Institute of Medicine) are 74 percent more likely to be unsuccessful at breast-feeding than mothers who observe these guidelines. However, women who are obese before pregnancy do not further increase their already high risk of lactation failure, regardless of their weight gain after conception. This suggests that obese women already have reached, before conception, a critical level of fatness for lactation failure. Whether and how long mothers breast-feed is important because breast milk can protect children from a variety of childhood illnesses. The United States public health goals, spelled out in *Healthy People 2010*, call for 75 percent of America's new mothers to start breast-feeding, 50 percent to continue for six months, and 25 percent for 12 months. At the present time, 64 percent of women breast-feed right after pregnancy, but only 29 percent continue for at least six months. The researchers suspect the reasons why obese women have trouble breast-feeding are a combination of biological, mechanical, and psychosocial factors.

Robert Barker/CU



Jean-Pierre Habicht studies the effectiveness of interventions to improve the health and well-being of mothers and children, specifically the effect of two important federal food aid programs on diets of low-income children, including the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC).



**“A major approach to nutrition is through a life course perspective that recognizes the importance of genetic endowment and its varied expression in the individual depending on the environment encountered from conception to death.”**

Researchers in the Division of Nutritional Sciences also study the effectiveness of interventions to improve the health and well-being of mothers and children. Jean-Pierre Habicht and collaborators examined the effect of two important federal food aid programs on the diets of low-income children. Preschoolers whose families get federal food aid have healthier diets than low-income children whose families are not getting assistance, and federally aided children are protected from iron and zinc deficiencies. In addition, the study shows that the benefits to young children from direct food aid through the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC program) are greater than if the families are given a cash allowance. The researchers found that preschoolers in the WIC program received 17 percent more of the recommended daily allowance, or RDA, for iron than nonparticipating low-income children and 10 percent more of the RDA for zinc in their diets. They also show significant boosts of eight out of 13 other nutrients studied. These benefits were realized without undesirable increases in fat, saturated fat, or cholesterol. The iron and zinc benefits from these programs are particularly important because iron deficiency is the single most prevalent nutritional deficiency in the United States, with up to 20 percent of low-income preschoolers less than 2 years of age suffering from anemia. Zinc is also important because other studies suggest that zinc deficiencies are related to growth retardation.

The determination of growth retardation in young children has been one of the most powerful tools for assessment of health status worldwide. Comparing a child's weight or height to a reference growth chart has been common practice in pediatrician's offices for generations. Because under-nutrition has such a profound effect on the growth of infants and young children, substandard growth is widely used to assess nutritional status and as a criterion for recommending changes in infant feeding practices. However, millions of healthy infants may be assessed as growing too slowly because of inadequate international child growth standards. As a result, many infants are taken off breast milk and given solid foods before they need them, with potentially life-threatening consequences.

Cutberto Garza and Edward Frongillo participate in a research project sponsored by the World Health Organization (WHO) and United Nations University to develop new international growth references that correct these problems. Garza chairs the steering committee that oversees the six-country effort, and Frongillo is a member of the technical advisory group. Although current growth references for young children have

served many useful purposes, they have a number of serious drawbacks. For one, they are not suitable for healthy infants around the world whose caregivers follow current WHO recommendations on infant feeding—that infants should be exclusively breast-fed for six months, and breast-feeding should continue through the second year or beyond with appropriate complimentary food added to the diet.

The current international growth reference is based on healthy children from the United States who were predominantly formula-fed and whose growth patterns are distinctly different from that of breast-fed infants following the WHO guidelines. It is well known that health workers, using the current growth references, too easily make faulty decisions regarding the adequate growth of breast-fed infants, and therefore they mistakenly advise mothers to supplement unnecessarily or to stop breast-feeding altogether. Given the health and nutritional benefits of breast-feeding, which include helping to prevent severe infectious and potentially fatal diseases, this misinterpretation of the growth pattern can have dire results. The project, which is a large multicenter project, should result in a new growth reference by 2003.

While research in maternal and infant nutrition represents a significant part of the Division's interest and expertise, there are equally strong research initiatives that deal with nutritional influence on chronic disease, the functional consequences of moderate undernutrition, the delivery of effective nutrition programs and interventions, and the resolution of nutrition problems through research-supported government policy in the United States and abroad.

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Edward Frongillo, along with Cutberto Garza, is developing new international growth reference standards to better determine growth retardation in young children worldwide.



**For more information:**  
<http://www.nutrition.cornell.edu>