

SOLANO COMMUNITY COLLEGE



3 7045 00042 5407



Digitized by the Internet Archive
in 2024

<https://archive.org/details/maternalnutritio0000shan>

MATERNAL NUTRITION AND CHILD HEALTH

627.6
•M34
SS3
2000

Second Edition

MATERNAL NUTRITION AND CHILD HEALTH

By

**DOUGLAS R. SHANKLIN, M.D.,
F.R.S.M.**

*Professor of Pathology and Obstetrics and Gynecology
University of Tennessee, Memphis
Memphis, Tennessee*

*Formerly, Professor of Obstetrics and Gynecology and
of Pathology, University of Chicago, and
Pathologist in Chief, Chicago Lying-in Hospital*

With a Foreword by

**BILLY F. ANDREWS, M.D., F.A.A.A.P.,
F.A.C.P., F.R.S.M.**

*Professor and Chairman Emeritus
Department of Pediatrics, University of Louisville
Louisville, Kentucky*



Charles C Thomas
PUBLISHER • LTD.
SPRINGFIELD • ILLINOIS • U.S.A.

347
B4T

Published and Distributed Throughout the World by

CHARLES C THOMAS • PUBLISHER, LTD.
2600 South First Street
Springfield, Illinois 62704

This book is protected by copyright. No part of it
may be reproduced in any manner without written
permission from the publisher.

©2000 by CHARLES C THOMAS • PUBLISHER, LTD.

ISBN 0-398-07074-1 (cloth)
ISBN 0-398-07075-X (paper)

Library of Congress Catalog Card Number: 00-023479

With THOMAS BOOKS careful attention is given to all details of manufacturing and design. It is the Publisher's desire to present books that are satisfactory as to their physical qualities and artistic possibilities and appropriate for their particular use. THOMAS BOOKS will be true to those laws of quality that assure a good name and good will.

Printed in the United States of America

MM-R-3

Library of Congress Cataloging-in-Publication Data

Shanklin, Douglas R.

Maternal nutrition and child health / Douglas R. Shanklin ; with a foreword by Billy F. Andrews.—2nd ed.
p. ; cm.

Includes bibliographical references and index.

ISBN 0-398-07074-1 (cloth) — ISBN 0-398-07075-X (paper)

1. Fetal malnutrition—Complications. 2. Malnutrition in pregnancy—Complications. 3. Brain-damaged children. 4. Birth weight, Low. 5. Infants—Nutrition. I. Title.

[DNLM: 1. Nutrition—Pregnancy. 2. Child Development. 3.

Fetal Diseases—etiology. 4. Infant Nutrition. 5. Nutrition

Disorders—complications—Pregnancy. WQ 175 S528m 2000]

RG627.6.M34 S53 2000

618.3'2—dc21

00-023479

For Sandy
1958–1997

FOREWORD TO THE SECOND EDITION

We have waited a score years since the first edition of *Maternal Nutrition and Child Health* was published in 1979. It was an excellent compendium of information for all who were interested in maternal, infant, and childhood nutrition. This interest in the influence of nutrition in all aspects of the developing embryo and fetus has provided the stimulus for much continued basic and clinical research, with emphasis, especially, on the development of the brain, teratology, and eventual outcome in postnatal life. New information gained from recent vitamin, amino acid, lipid, and carbohydrate basic studies, and endocrinological, pharmacological, and disease states upon metabolism and energy requirements at special points in pregnancy and infancy are welcomed. This information must be made available especially to the medical profession and nutritionists, and as much useable information as possible conveyed to the educational system of our country. The mothers and infants of today and tomorrow will benefit only through personal knowledge of these things.

Professor Douglas R. Shanklin will again be appreciated for collating, selecting, and questioning the available information from the broad expanse of both basic and clinical nutritional literature. His comments upon this subject are expertly and clearly stated and enhanced from his wide experience and knowledge of the physiology and pathology of pregnancy and infancy as a developmental, obstetrical, perinatal, and neonatal pathologist of world renown. Importantly, subjects from the first edition are challenged and emended to include recent and current research and experience. Two new chapters have been added to assess important programs of nutritional supplementation and management of human pregnancy. Emphasis here is on protein-calorie balance and a growing awareness of trace nutrients such as vitamins and minerals.

Professor Shanklin is again to be congratulated for this work. His tremen-

dous efforts over the past six years to gather and update this information will be greatly appreciated. This book should be read often and most carefully; it is an excellent resource.

BILLY F. ANDREWS, M.D.

FOREWORD TO THE FIRST EDITION

It is fortunate for the future of the human species that a proper awareness has evolved during the last decade or so in the scientific community and the medical profession for adequate maternal nutrition during pregnancy and lactation and infant nutrition during the first most important years. Nutritional deprivation imposed either prenatally or during the early postnatal period can affect the initial development of the brain, which may result in permanent and irreversible damage to its functional capacity. More than three-quarters of the world population live in underdeveloped parts of the world where the mothers and infants do not receive adequate food during critical periods of development of the baby and are thus deprived of the opportunity to grow to their full potential. Whereas some damage is done by inequitable distribution of available food and affliction from the curse of poverty, damage is also caused by ignorance on the part of parents and lack of appreciation on the part of health personnel of the importance of good nutrition during the early stages of development.

The monograph of Professor Douglas R. Shanklin and Mr. Jay Hodin on the role proper nutrition plays in maternal and child health is very timely in its presentation and emphasis. One may have some excuse to defend the poor state of maternal nutrition and child health in the less developed countries of the world, but one is hard pressed for a valid excuse to defend the poor nutrition of the mothers and infants in an affluent country such as ours. Some readers may be aware of the efforts of Doctor Tom Brewer and the Society for the Protection of the Unborn through Nutrition, directed to the medical community, to pay special attention to the diet of the pregnant mother. The scientific studies reviewed in this work represent the basis for his efforts.

Episodes of malnutrition leave permanent deficits in the physical and mental development of the individual that may not be corrected by later

nutritional rehabilitation. The growth retardation caused by maternal malnutrition during pregnancy and early lactation could have more severe consequences in terms of mental development and learning potential than malnutrition of the infant in the postnatal period. School lunches, giving nutritionally balanced meals to the kindergarten and school children, may come too late and may not be able to reverse the deficits in behavioral and intellectual capacity caused by nutritional insults in the perinatal and early postnatal periods.

Poor environments contribute heavily to behavioral deficits, but one must not discount the role of nutrition in the perinatal period when the influence of a nonstimulating environment may not be apparent. A child well nourished *in utero* and early postnatal life may not suffer from the retarding effect of poor environment, but a malnourished child easily falls prey to a nonstimulating environment that may damage intellectual potential.

In this book, the authors have done an excellent job in the collection and compilation of pertinent information on the nutrition of the pregnant woman and its influence on the offspring. They have covered prenatal to early childhood nutrition and have included sections of physiological, neurological, and behavioral abnormalities which are correlated with aspects of malnutrition. Those interested in the role of nutrition on reproduction will also find a mass of valid scientific data from studies of human development. Written in simple language, the book is a forceful presentation on the subject and will be stimulating reading for both the professional and the layman.

S. L. MANOCHA

PREFACE TO THE SECOND EDITION

The first edition of this book came out six months prior to the formation of a Special Advisory Panel for the congressionally mandated National WIC Evaluation to be managed by Research Triangle Institute for the Food and Nutrition Service of the U.S. Department of Agriculture. One consequence of this was that the senior author of *Maternal Nutrition and Child Health* was appointed to the Panel and became its Convenor/Chairman. This is an appropriate place to say this of my colleagues in that six-year endeavor, I have not yet again had the benefit of any other committee or group with the same high professional dedication, collegiality, and scope of expertise which our diverse, almost divergent, backgrounds brought to bear on the endeavor in such a compellingly synergistic way. The Panel consisted of Catherine Cowell, Ph.D., nutritionist; Stefan Harvey, an advocate for children's issues; Robert Kane, M.D., then of the Rand Institute; David A. Kenny, Ph.D., a statistician in a department of psychology; Janet King, Ph.D., nutritionist; Milton Z. Nichaman, M.D., School of Public Health, University of Texas, Houston; and David Paige, M.D., a pediatrician with the School of Public Health, Johns Hopkins University; and myself.

It has been 14 years since the group was disbanded and a final report issued by the Institute and their ultimate principal investigator, David Rush, M.D. Certain details of this endeavor have been collated into a brief chapter in this second edition. The effort and the result have to be viewed now in the light of much which has appeared since both the first edition and the National WIC Evaluation. It may well be that another survey of nutritional practices of the United States at large, as well as in pregnancy and early neonatal life, is warranted. If so, then the manner, scope, and objective will be very different, as parts of this book will make clear.

The first edition of *Maternal Nutrition and Child Health* was written to provide the basis for countering the studied nonchalance then prevalent

within the medical and other health care professions toward pregnancy nutrition. One putative measure of the "success" of prenatal care is the perinatal mortality rate which has fallen in the United States in recent years. Were that this was so! The perinatal mortality rate has fallen in large measure because of the enhanced capabilities of *neonatal* care. Meanwhile, the prevalences of preterm birth and lack of prenatal care for an important segment of the American population remain high.

This seeming paradox required, in the mind of this author, for a revision of *Maternal Nutrition and Child Health* in two directions simultaneously to seek: (1) a better connection with basic work on aminoacids and protein metabolism, and (2) better *biological* understanding of the outcome of clinical events and in surveys. The last twenty years have shown a marvellous complexity to many aspects of biology and human pathophysiology in such areas as cytokines and cellular signal transduction. There are signs this level of analysis is beginning to affect nutritional science in basic ways. The progress of cell biology is, to some degree, accelerating; if this becomes true of nutrition as applied to human pregnancy, then any prospective third edition of this work cannot be put off for an additional twenty years! The work of the past twenty years has brought home a lesson: there are biological limits to the capacity of the pregnant woman to assimilate food just as there are very particular requirements to protein synthesis. There are two very fundamental principles which have to be recognized and honored as the effort is made to comprehend the growth and maturation of the fetus. The first is: proteins are simultaneously the structure and the ultimate functionality of a fetus in preparation for transition to postnatal life. The second is: there is an energy cost to the process both over time and at every point in time. Knowing the optimum amounts of substrate and the optimum coordination of these principles at work are the objectives of any biologically-based study of human nutrition.

At the same time, one has to keep in mind that pregnant women eat food, not nutrients in the particulate sense. It now seems fairly clear that the fetus, through placental metabolism, "eats" nutrients but not foods, in the assimilative sense. When considered as a vector equation, this relation is unidirectional but also a complex of parallel tracks. What remains to be elucidated is the comparative efficiency of the several tracks as well as the whole. Outcome can be defined, from within this matrix, in more than one way. Absent further data and clarification of the process, we have to conclude, however tentatively, there is no readily applied single or overarching outcome measure. This is one part of the fault of much recent epidemiologic investigation, a fault which is best repaired by greatly enhanced basic cellular nutrition from which the correct questions can be

framed.

Thanks are due to several colleagues for assistance beyond all measure in obtaining the more recent literature of basic and clinical nutrition, especially Patricia A. Pratson and Heidi Nelson of the library at Marine Biological Laboratory, Woods Hole, Massachusetts. Marion E. Freeland, Gainesville, Florida, made the medical library at the University of Florida a second home and converted the first edition to computer-based text for editing and expansion. Her contribution was essential in every way.

My appreciation and thanks go to Henrietta Bada-Ellzey, M.D., currently, and Susan E. Carlson, Ph.D., formerly, of the Neonatal Intensive Service of the Regional Medical Center (Departments of Pediatrics and Obstetrics and Gynecology, University of Tennessee, Memphis) for many discussions over many years, and to F. Curtiss Dohan, M.D., Chief, Neuropathology, University of Tennessee, and to my cousins, Barbara and Peter Watts, Waterbury Center, Vermont, for several critical and valuable suggestions. I would be greatly amiss if I did not note the valuable, if inchoate, contribution of the dozens of second-year medical students in my courses on the pathology of pregnancy and the newborn at the University of Tennessee, Memphis, these past several years. They made important contributions, through their questions, especially on the important subject of lactation.

DOUGLAS R. SHANKLIN

PREFACE TO THE FIRST EDITION

The relationship between nutrition, especially during the prenatal period, and child mental and physical health is demonstrated to be causal and highly correlated. Some of the studies indicate that there is less than one chance in a billion that prenatal nutrition does not influence the newborn's health and subsequent mental and physical development. In addition, neurological abnormalities, such as mental retardation, cerebral palsy, and epilepsy, which have traditionally been ascribed basically to genetics or unknown causes, are linked in large part to malnutrition during the most rapid, critical periods of development.

A continuum of reproductive casualty, defined as spontaneous abortion, perinatal death, cerebral palsy, epilepsy, mental retardation, hyperkinesis/learning disabilities, and minor neurological disorders, can be caused by varying degrees of prenatal malnutrition; that is, spontaneous abortion is caused by severe malnutrition, whereas minor neurological impairment is more likely to be caused by a much lesser degree of malnutrition.

Mental subnormality caused by prenatal malnutrition can be manifested as brain cellular dysfunction or underdevelopment, both of which occur primarily during the intrauterine stage of development. Most neurologists believe that brain underdevelopment, which is characterized by a marked deficiency in the normal number of brain cells rather than a reduction in their size, usually occurs concurrently with cellular dysfunction. This impairment of the functioning of the central nervous system can frequently be ascribed to synaptic and dendritic dysfunction, the prime cause of neurological abnormalities. Since a newborn's brain is developed to approximately 60 percent of the adult capacity, a deficiency of brain cells usually cannot be reversed.

The majority of instances of irreversible brain damage occur during the

prenatal period or, less frequently, during delivery. Damage to the fetal brain is frequently exhibited by a histological lesion. Infants born with such a lesion, primarily caused by a lack of energy resource, or vascular incidents, are overproportionately afflicted with either mental retardation, cerebral palsy, or epilepsy. Complications during the prenatal period or delivery resulting from the placenta being extensively infarcted, abnormally small, or not firmly implanted in the uterus, which are unlikely conditions among well nourished women, can also lead to brain damage by depriving the unborn of oxygen or other nutrients during the prenatal period or birth process.

The relationship between maternal complications and neurological disorders of childhood is extensively explored. Maternal health, which is profoundly affected by nutritional status, is shown to be a fairly reliable indicator of infant and child health.

Since birth weight is probably the most accurate of all available prenatal and paranatal variables, the causal relationship between birth weight and prenatal nutrition has been extensively documented. Birth weight has also been found to correlate highly with infant survival and cognitive potential. Numerous longitudinal anteroseptive and retrospective studies are cited to demonstrate that children of subnormal birth weight are prone to develop neurological abnormalities.

To provide practicality, the effects of applied, scientific nutrition on maternal and infant health are discussed. In addition, the means by which the current medical practices of restricting the salt intake and weight of pregnant women and administering hazardous drugs that cause permanent mental and physical impairment are researched. Lastly, the effects of poor nutrition during infancy and early childhood on limiting growth and development are documented. Substandard nutrition during the first few years of life is shown to retard or impair the growth and functioning of individual brain cells, which frequently predisposes to permanent mental impairment.

We are deeply indebted to Regina Gamble, Diane Langowski, Linda O'Donnell, and Sophie Ryczko for their invaluable assistance in editing the manuscript. We thank Marion Freeland for aid in completing the bibliography. Thanks for excellent aid are also due Alfred Klinger, George Mark Hodin, Benjamin Pasamanick, Ellen Peroutka, the late Francis Bayard Carter, and the late Robert A. Ross.

DOUGLAS R. SHANKLIN
JAY HODIN

CONTENTS

<i>Foreword to the Second Edition</i>	vii
<i>Foreword to the First Edition</i>	ix
<i>Preface to the Second Edition</i>	xi
<i>Preface to the First Edition</i>	xiv
<i>Chapter</i>	
1. INTRODUCTION	3
2. THE EFFECT OF STARVATION ON REPRODUCTIVE CASUALTY	12
3. THE INFLUENCE OF PRENATAL NUTRITION ON MATERNAL AND INFANT HEALTH	24
Basic Animal Nutritional Research	24
Prospective Noninterventional Studies in Humans	26
Effect of Nutrition on Birth Weight	30
The Montreal Diet Dispensary Nutritional Program	33
Prospective Interventional Effects on Maternal Nutrition	37
Retrospective Studies	52
The Vanderbilt Cooperative Study	55
4. THE MOTHERWELL PROTOCOL	58
The Assessment Method	59
Management of Labor and Delivery	62
Abdominal Delivery	64
The Aberdeen University Review Project	66
5. PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL EFFECTS OF MALNUTRITION	71
Malnutrition and Impaired Brain Development	71

Malnutrition and Placental Pathology	77
Consequences of Sodium Deficiency	82
Pathogenesis of Gestosis	94
Low Umbilical Cord Protein and Respiratory Distress Syndrome	101
Carbohydrate Intolerance, Hyperinsulinism, and Gestosis	102
Evidence from the Diabetic State	104
The Australian Protocol	113
Indirect Evidence of Adverse Effects of Malnutrition	115
6. BIRTH WEIGHT AND DEVELOPMENT	124
Retrospective and Anterospective Studies	125
The Womens-Infants-Children Protocol (WIC)	144
Gambian Studies	154
7. THE CORRELATION OF PRENATAL AND PARANATAL COMPLICATIONS WITH NEUROLOGICAL DISORDERS	159
Factors Associated with a Continuum of Reproductive Casualty	166
Interracial Differences in Reproductive Casualty	171
The Relation of Standardized Prenatal Care without Proactive Nutritional Aspects	176
Association of Mental Deficiency with Low Birth Weight and Complications of Pregnancy	178
Relationship Between Low Birth Weight and Neurological Damage and Mental Deficiency	179
Complications and Low Birth Weight Associated Reading Disorders	184
8. THE RELATION OF MATERNAL HEALTH TO INFANT HEALTH AND DEVELOPMENT	188
Maternal Complications	191
Dependent and Independent Associations of Birth Weight with Demographic Factors	196
Significance of Prepregnancy Weight and Weight Gain During Pregnancy	197
Outcome Measures in the Motherwell Protocol	204

9.	NUTRITION DURING INFANCY AND EARLY CHILDHOOD	210
	Retrospective Nutritional Studies	211
	Effect of Malnutrition on Lactation	215
	Effect of Food Intake on Brain Function	221
10.	THE BIOLOGICAL IMPERATIVE	223
	The Genetics of Toxemia and Birth Sequences	228
	Maternal Metabolic Compartmentalization	231
	Nutrient Intake Efficiency	234
	Afterword	239
	<i>References</i>	243
	<i>Index</i>	275

MATERNAL NUTRITION AND CHILD HEALTH

Chapter 1

INTRODUCTION

PROPER NUTRITION, especially during pregnancy, is of paramount importance. Reference to the need for good nutrition for pregnant women extends at least as far as the Bible. One passage in Judges reads, “Neither let her drink wine or strong drink nor eat any unclean things” [590].

Inadequate nutrition during pregnancy has been linked with a continuum of maternal and infant morbidity and mortality. A deficiency of one essential nutrient, even if all other nutrients were adequately supplied, can result in a miscarriage, perinatal death, or the birth of a developmentally disabled child [49,117, 252,324,502,620]. Indeed, folic acid supplements will be required to prevent the estimated 4,000 cases per year of neural tube defects, from spina bifida to anencephaly [619]. Pregnancy outcome is improved by supplemental micronutrients, multivitamins, and minerals [476].

Similarly, excess of a single nutrient may modulate effects of a deficit of another metabolite, in this case the “nonessential” amino acid, alanine [581]. There are several metabolic disorders, difficulties catabolizing branched chain amino acids (e.g., maple syrup urine disease, propionic acidemia, isovaleric acidemia, and methylmalonic acidemia), which require protein restricted diets as leucine, isoleucine, valine, and other precursors to propionate have to be restricted. Alanine has been shown to decrease protein requirements in such children, modulating adverse effects of the disordered metabolism [282,571,581].

Nonketotic hyperglycinemia [142,358,548] and glutaric acidemia [101] are examples of the injurious effects of unbalanced excess of an amino acid or close metabolites.

These are all rare conditions. They are lessons of nature which remind us of the subtle complexity in the nutritional and metabolic machinery of the

body, with interactions between the background genetic matrix, the specifics of metabolic physiology, and the available foods and factors from the maternal and outside environments.

Numerous prospective and retrospective epidemiological and experimental studies, some reviewed here, support the general inferences which follow from these kinds of reports.

Severe malnutrition, as evidenced by retrospective studies of childbirth during World War I, causes amenorrhea [11,249,503]. When conception results, malnutrition can cause (in order from severe to lesser degrees of reproductive wastage) maternal death, fetal and neonatal death, congenital anomalies, cerebral palsy, epilepsy, mental retardation, behavioral disorders, or spontaneous abortion.

Although there is only limited research on the *direct links* between prenatal malnutrition and developmental disabilities, there is a wealth of data demonstrating the relations between inadequate nutrition, infant death, and low birth weight, which predisposes to neurological abnormality.

Infant mortality, more than 60 per cent higher in the United States than in some other advanced nations [598] (where pregnant women are taught better dietary habits, among other differences), provides a useful first approximation of the prevalence of developmental disabilities. Margaret and Arthur Wynn stated:

One official government (Finland) estimate assumes that two children survive so severely and permanently handicapped as to become a charge to the state for every one who dies, and that reducing the causes of death does on the average reduce the numbers that are handicapped in the same proportion. Mortality rates are an indicator not only therefore of infant loss but of infant damage . . . The prevention of handicap is much more economic, as well as more humane, than failure to prevent followed by care services and subsidies to the handicapped. [574].

This admirable objective has to be put back into the context of the United States in 1999: over 44 million medically uninsured persons and an increasing prevalence of low birth weight [570,609]. It remains to be seen whether the premise of the Wynns will hold in the United States, where infant and maternal mortalities have reached historic lows, with some further room for improvement [620].

The relationship between malnutrition and developmental disabilities, which is established physiologically, clinically, and epidemiologically, is strengthened by their association with birth weight. As will be discussed, numerous studies have shown that maternal nutrition profoundly affects the child's birth weight [180], long accepted as the most accurate indicator of infant health and future mental and physical development [290]. Even though factors other than inadequate nutrition can reduce birth weight,

malnutrition is the primary cause of birth weight under 2500 grams (5.5 pounds). The author estimates, in the United States, at least three-fourths of examples of low birth weight are due to inadequate nutrition.

The prevailing nonchalance toward maternal nutrition is seen in the comparatively high American rate (1974: 7.7%) of low birth weight [601]. More recent data shows worsening of this key factor [568,609] despite lower overall infant mortalities [606,612,614,616]. The implications of this dichotomy for future neurological impairment should be obvious. The link between maternal and family socioeconomic resources and poor pregnancy outcome is painfully obvious in American public health data [410,616] (Tables 1-1 and 1-2).

Table 1-1
MATERNAL CHARACTERISTICS WHEN CONSIDERED
FOR WOMEN BELOW THE POVERTY LEVEL (SOCIAL
SECURITY ADMINISTRATION DEFINITION) [614]

<i>Maternal aspect</i>	<i>Percentage of women by poverty level</i>		
	<i>Below level</i>		<i>Above level</i>
Married	12.9	± 0.5	76.5
Unmarried	41.0	1.3	35.5
≤17 years	42.3	3.2	29.7
≥18 years	19.0	0.5	67.8
First prenatal visit			
1-3 months	14.9	0.5	72.6
>3rd month	37.3	1.3	44.1
Education ≤11 years	45.8	1.5	32.5
12	20.5	0.8	65.4
>12	6.8	0.5	83.4
White	16.0	0.6	71.6
Black	40.6	0.8	37.5

Numbers do not total to 100.0% due to omission of those not reporting; data are mean percentages ± S.E.M.

Surprisingly, the incidence of underweight births was no higher in the 1920s than in the 1970s [1,244,601,602,609]. From 1950 to the late 1960s, the low birth weight rate, which during the comparative period did not increase in any other advanced nation [340], rose 10 per cent [92]. Concurrent with an increased frequency of low birth weight was increased use of arguably unscientific obstetrical practices, such as weight control, salt restriction, and dangerous drugs [60,269]. The number of underweight births exceeded

240,000 annually in 1974 [601].

More recently, overall national rates of low birth weight rose in 1989-1991 after fluctuation in a narrow range from 1981 to 1988.

Table 1-2
SELECTED ANNUAL RATES, LOW BIRTH WEIGHT (LBW),
PER 1000 LIVE BIRTHS [609]

<i>Category</i>	1981	1986	1991
White LBW			
Term	24.4	22.9	22.0
Preterm	31.0	32.0	35.7
Total	55.4	54.8	57.8
Black LBW			
Term	52.3	48.6	47.2
Preterm	72.1	75.5	87.7
Total	124.4	124.1	134.9
Overall LBW			
Term	29.0	27.1	26.5
Preterm	37.5	38.9	44.3
Total	66.4	66.0	70.8

Totals may differ due to rounding.

Several nations have reduced their rate of underweight births to about a third of the rate in the United States. The rate of prematurity (commonly defined as low birth weight unless specified to mean an abnormally short length of gestation) had been reduced to less than 3 per cent by 1973 in the People's Republic of China, with infant mortality in some areas below 1 per cent [593]. Additionally, low birth weight incidence in some other advanced countries was approximately 3 per cent in the 1960s [1,294].

Low birth weight has accounted for two-thirds of postneonatal deaths [18] (deaths among liveborns occurring in the first 28 days of life). A 1968 Department of Health, Education, and Welfare study revealed that low birth weight babies have a neonatal mortality rate thirty times higher than that of infants of higher birth weight [583]. Low birth weight was the eighth leading cause of death in the United States in the early 1960s [1]. It no longer holds sway at these rankings because of the progressive skills of neonatologists and intensive care centers which have generated enormous costs [613], compounded in part because infant mortality is a more common outcome for pregnancies in women whose family income is below the poverty level [614] (Table 1-3).

This data furthers the linkage between maternal resources as proxy for nutrient intake and general pregnancy care, keeping in mind the relationship between infant mortality with disability and poor growth as "lesser" degrees

Table 1-3
INFANT MORTALITY RATES PER 10,000 LIVE BIRTHS,
BY RANK OF THE MOTHER RELATIVE THE POVERTY LEVEL
PER THE SOCIAL SECURITY ADMINISTRATION [614]

<i>Interval</i>	<i>Below level</i>	<i>Above level</i>	<i>Risk ratio</i>
<28 days	7.8	5.5	1.418
28-364 days	5.7	2.8	2.035
<1 year	13.5	8.3	1.626

of reproductive wastage.

The low birth weight child, as will be discussed in detail later, is especially susceptible to a multitude of neurological dysfunctions and other physical defects. The \$100 million National Institute of Neurological Diseases and Stroke's Collaborative Study of Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Childhood (Collaborative Study) showed that definite neurological impairment of children at one year of age was three and a half times higher among low birth weight children compared to high birth weight [228,229,402].

Chapters 13 and 14 of Hardy et al. [229] are the core of the book: Chapter 13, "Developmental Status at eight Months," and Chapter 14, "Neurological Status at One Year." The methodology was well laid out. Both sections of the Collaborative Study are descriptive, not predictive. As such, they serve a useful purpose in estimating the magnitude of the problem and the principal associations, some of which are antecedent. These do not carry pathogenetic insight. Lacking data on one of the most important environmental aspects of fetal development, namely, the state of maternal nutrition before and during pregnancy, no pathogenetic conclusions can be drawn.

Birth weight was directly related to IQ at age four [229,402]; up to half of all children underweight at birth have an IQ under 70 [229].

However, lest the magnitude and scope of the Collaborative Study be viewed as sufficient grounds on which to base either medical diagnosis or treatment or, in a larger sense, public health policy, the deficiencies of the program must be faced openly. The study has resulted in many papers and journal articles which will not be reviewed here, and two major reference books [229,402] which contain sufficient information for present purposes. Both are comprehensive reports. The earlier work, 1972, was lightly cited in the first edition of this book, including a brief critique in Chapter 7 (Chapter 8, this edition). The index failed to list nutrition as a topic and the only index entry applicable to the nutritional status of the pregnancies is barely one text page on anemia (bottom of page 238, upper 70% of page 239; ironically, there is an inversion of text paragraphs as well [402]).

More specifically, this is an account of the lowest hemoglobin level which was available for about 70 per cent of white gravidas and 75 per cent of black women. Far fewer hematocrit levels were available for study, 29 and 24 per cent respectively [402].

The second volume, a study of the infants at one year of age, was published in the same year as the first edition of this book (1979), each set of authors unaware of the imminent publication of the other. In similar fashion, Hardy, et al. [229] brought forth a detail laden work with an index which *fails to list* nutrition as a topic. The only index entries applicable to the nutritional aspects of the matter are hematological observations, including hemoglobinopathies manifest in the first year of life (pages 93-100, 277, 280 cite [229]).

Low birth weight infants are prone to mental and motor impairment, high bilirubin levels, and are more susceptible to deafness [229,231,344]. It is not surprising that many develop kernicterus, a factor in the development of deafness as well as the degeneration of nerve cells [3].

One study of eight- to ten-year-old children showed abstract verbal reasoning and perceptual/motor integration were more related to birth weight than to IQ [559]. Many of the 20 million Americans with severe handicaps in 1972 [402] were underweight at birth. One extensive study of recipients of Social Security funds for disability before age eighteen found that 75 per cent had prenatal origin [583]. The abnormality was neurological in 94 per cent.

The 1962 President's Panel on Mental Retardation report, *National Action to Combat Mental Retardation*, stated that it is necessary to ". . . explore the possibilities and pathways to prevent and cure mental retardation..." [259]. One of the principal findings was that the ". . . prevalence of mental retardation (in children) tends to be highly associated with lack of prenatal care, prematurity, and high infant death rates."

The 1974 *Prevention Handbook*, a publication of the National Association for Retarded Citizens, stated, "Prematurity is the most important obstetric factor contributing to mental retardation" [594]. There is evidence that premature infants may be ten times more likely to develop mental retardation than full-term infants [253]. Reducing the incidence of low birth weight in the United States from the 1979 rate of 8 per cent to a projected 2 per cent, a level which will later be shown to be obtainable by ensuring every pregnant woman adequate nutrition, would result in an immediate reduction in the incidence of mental retardation by at least one-third, if not more. We now know, to the contrary, that this basic goal has receded even further [609].

An analysis of national nutritional data, in the *New York Times*, showed that the health and development of more than one million unborn fetuses are

substantially compromised by prenatal malnutrition every year in the United States [474]. The annual number of miscarriages, the incidence of which is causally related to nutritional deficiencies [135], is not easily ascertained directly. When the minimum frequency of 11.8 per cent [512] is applied to the number of births in the United States [604], the estimated eight-year annual average for 1990-1997 would be 471,604.

Our current toxic environment has in it many substances which are adverse to the integrity of early pregnancy, with an increase in the rate of miscarriage, including cocaine and tobacco [397,540,546].

Platt, who documented the pernicious effects of intrauterine malnutrition on the developing central nervous system, stated:

With the present state of knowledge, it must be accepted that protein-calorie deficiency, with its attendant ills, may lower maternal efficiency and lead to the production of underweight babies, many of whom will die before reaching two years of age, whilst amongst their survivors there will be some who never reach their full physical or mental potential . . .

Platt and Stewart offered this thought: When all infants are given equal conditions both within and outside the womb, it is likely many so-called racial characteristics will disappear [422].

One of the tasks of this second edition is to test these ideas in the crucible of human biology. There is one factor which seems to have been ignored mainly despite the clarity of the data [307]. Langlois reported measurements on over 1300 hysterectomy specimens and sought to correlate the findings with gravidity, parity, age, and race. In brief, gestational growth of the uterus in black women is proportionately less than in white women. The details and implications of this remarkable finding are discussed in Chapter 8.

The factors which influence fetal growth and development and the eventual progress of childhood are legion. In the twenty years since the first edition of this text, many significant changes have occurred and some wholly new factors have come into play. New diseases have been recognized. Some, like the acquired immunodeficiency syndrome (AIDS), which follows infection with human immunodeficiency virus (HIV), have come to involve large numbers of women, estimated for 1994 to be 100,000 of reproductive age [608]. There were 80,000 deaths of women from AIDS between 13-49 years over the 13-year period, 1985-1997 [587].

Vertical transmission of HIV to the fetus *antepartum* or the newborn *intrapartum* has brought with it the added risk of powerful medications such as zidovudine [608,610]. Nevertheless, zidovudine treatment resulted in a 67.5 per cent reduction in the vertical transmission rate [608] and was thereafter recommended for general use.

The year 1979 saw the third of a now continuous span of 21 years with

over a million pregnancy terminations each, some known to be anomalous or to have specific adverse genetic factors. Despite progressively greater median age for first marriage for both men and women, reaching 25.0 years for women in 1997, over half of all pregnancy terminations occur in women *under 25 years* (in 1992, this was 54.75 per cent [618]). This affects the prevalence of birth defects, discussed in more detail in Chapter 7.

Recognition of the fetal alcohol syndrome has grown significantly. This makes it somewhat difficult to be sure whether the increase from a baseline in 1979 of 1.0/10,000 pregnancies to 3.7/10,000 in 1992 is ascertainment related in whole or just in part [607]. Other forms of pharmacologic abuse are rampant. Cigarette smoking declined from 1985 to 1997 for women in the age range 12-34 years [596], but the percentages of high school seniors for "ever used" substances of abuse remained shockingly high for marijuana/hashish, inhalants other than amyl and butyl nitrites, hallucinogens, crack cocaine, heroin, other opiates, stimulants such as amphetamine, sedatives including barbiturates, tranquilizers, alcohol, and cigarettes as the source of nicotine[591].

Despite progressively falling overall infant mortality rates, down to 7.1/1000 live births for 1997 [605,620] (the rate for blacks remains over twice the rate for whites), the United States ranked 24th in 1990 for nations with at least one million population [612]. This is worse than in 1980 when the United States ranked 20th!

The best to be said for this dismal record is that it allows substantial room for improvement. A thesis of this second edition is that data analysis has often arrested at first phase statistics when pattern analysis is more likely to produce a picture with at least semiquantitative understanding. Many recalculations of published data which appear in the text to follow will illustrate the force of this distinction. David Hilbert (1862-1943), one of the great mathematicians and logicians of history, propounded the following operational axiom in 1900 [48]:

If we do not succeed in solving a mathematical problem, the reason frequently consists in our failure to recognize the more general standpoint from which the problem before us appears only as a single link in a chain of related problems.

We have but to substitute the words *nutritional and developmental* for *mathematical* in Hilbert's statement to incorporate it into the problems we face in this book. It is not necessary to appeal to the rules of symbolic logic or to the tenets of complexity theory[550] to appreciate the validity of this approach, or for its putative practicality. It is only necessary to remember the embryological journey the zygote takes to become an integrated, maturing child.

Very recently, the popular press has linked some late life health events to intrauterine conditions [542]. Perhaps, similar constructive publicity will assist the need for improved education in and understanding of the importance of maternal nutrition.

Chapter 2

THE EFFECT OF STARVATION ON REPRODUCTIVE CASUALTY

DURING THE SIEGE of Leningrad by the Germans during World War II, birth weights declined precipitously, with a companion increase in mortality and morbidity [11]. The rates of stillbirth, infant mortality, low birth weight, substandard birth length, and morbidity all increased dramatically as a result of the 17-month siege.

Reflected in that period of near starvation and other harsh conditions, including no heat in many homes while temperatures plummeted as low as 40 degrees below zero, no transportation, and extreme physical exertion, were also sharp increases in amenorrhea, lack of conception, and, probably, spontaneous abortion. A most dramatic decline in births to 79 in one large clinic in Leningrad during the second half of 1942 (there were 1,639 births in the same clinic in the latter half of 1940) was primarily due to the fact that hunger, rampant throughout most of the siege, was most pronounced from November 1941 through January 1942. Since most births in the first half of 1942 were conceived prior to the siege, which began in August 1941, there were substantially more births during the first half of the year (416) than during the latter half. The decline in births to 493 for the entire year of 1942 represented a significant decrease from the average annual number of births in the same clinic in the previous three years, which was 3,867 ($p<0.0001$).

Among infants whose birth weights were recorded and at least 47 cm long at birth, the 255 infants born in the first half of 1942 weighed an average of 585 g less than the 1,807 infants born during the first half of 1941. Of the 368 of 391 live births (there were 23 stillbirths) weighed at birth during the first half of 1942, 49.1 per cent weighed under 2,500 g; only 3.6 per cent weighed over 3,500 g. Similar decreases in birth weight were also recorded in other

clinics in Leningrad during the same period. Antonov quoted six studies analyzing the profound effect of hunger on birth weight during World War I in Russia that confirmed his direct observations and interpretations.

In addition, the prevalence of live births in the clinic less than 47 cm long at birth was 41.2 per cent during the first half of 1942 but only 6.5 per cent during the second half of the year. One of the most significant findings was that the rate of stillbirths and neonatal deaths was more than three and a half times as high during the first half of 1942 (256/1,000) as during the second half of the year (70/1,000).

The large majority of the women who gave birth in the second half of 1942 were much better nourished than those in the first half of the year (51 were known to have and many others were suspected to have received large rations). For this reason, the rates of stillbirth and low birth length were approximately normal. The marked increase in birth weight among the 79 births during the latter half of 1942 appears to be largely attributable to the general improvement of food availability and quality during the last few months of the year. Additional documentation of the effect of nutrition on birth weight, particularly during late pregnancy, is in Chapters 3 and 6.

The strikingly high rates of mortality and morbidity can also be attributed to prenatal and postnatal hunger, inadequate medical facilities, the lack of heat, and other debilitating factors. Most infants were fed artificial formula because hunger interferes with lactation. Dairy milk was not available. Among the births in 1942, nearly 89 per cent of the infants lost weight for more than three successive days after birth; the average loss of weight among all infants amounted to 9.7 percent. Considering the pernicious living conditions were most severe during the first part of 1942, it is not surprising that nearly 26 per cent of all infants born during the first six months of the year died during that period. In all clinics in Leningrad, the incidence of infant mortality in 1942 ranged from 12 to 32 per cent among infants of normal birth length (≥ 47 cm) and from 50 to 80 per cent among those of subnormal birth length. The morbidity in 1942 among infants born in the aforementioned clinic was 32.3 per cent. Most of the morbidity and mortality was attributed to pneumonia and scleredema. In addition, numerous instances of congenital softening of the skull bones, wide fontanels, open sutures of the skull, and other previously rare disorders were observed.

Antonov stated:

Hunger, vitamin deficiency, cold, excessive physical strain, lack of rest, and constant nervous tension had their effect on the health of the women, the intrauterine development of the fetuses, and the condition of the newborn children during the siege . . . The cause of the unusually high proportions of

premature births (defined as births under 47 centimeters in length) and of stillbirths in the first half of 1942 was hunger during pregnancy, that is, the insufficient quantity and the unsatisfactory quality of the women's food. [11]

A similar case, the mass starvation period during the winter of 1944 to 1945 in Holland, resulted in smaller infants and higher rates of mortality and malformation, even though the general state of nutrition was adequate or near adequate during periods immediately preceding and following that winter [503]. During the most severe starvation, half the women of child-bearing age had amenorrhea. As in some clinics in Leningrad, the number of births declined by at least 80 per cent from antebellum times [11,503].

During the most limited rationing, the approximate daily intake of calories by pregnant women was said to have declined from 2,300 to 731 and that of protein from 67 to 24 g [505]. However, in some areas, diets of pregnant women remained fairly adequate. Infants born during the hunger period were significantly shorter than those born when intrauterine growth was not affected by the wartime starvation. Offspring born during the war weighed an average of 240 g less than prewar babies.

Unfortunately, statistics of the incidence of developmental disabilities of children born during the war are not available. However, these abnormalities seem to increase more dramatically than mortality and malformation [574]. Recently, however, Susser and Lin [517] examined subsequent adult hospital admissions for schizophrenia. They noted the western region was more affected by the famine (<1000 kcal per diem). Hospital records from this region were surveyed (Table 2-1).

Table 2-1
ENERGY INTAKE CORRELATED WITH TIME FRAME,
THE DUTCH HUNGER WINTER, 1944-1945 [517]

<i>Ration (kcal)</i>	<i>Time period</i>
<1000	August-December 1944
1000-1500	March-July 1945, January 1946
>1500	All other months, 1944 and 1946

The paper reports energy sources in kilojoules (kJ);these are converted for textual consistency; convert by 1 kJ = 0.238 kcal, often rounded to 0.24 kcal; also, 1 megajoule (MJ) = 240 kcal.

They found a substantial increase in hospitalizations for schizophrenia, but only in women. This seemingly curious finding is consistent with observed differences in assessed contributory factors and different profiles of the clinical presentation of schizophrenia between men and women [203]. The possibility of a prenatal factor in schizophrenia is enhanced by similar findings following pregnancies during an influenza epidemic [363].

To determine the influence of reduced dietary intake on neonatal death and low birth weight, Dutch vital statistics were examined in one clinic in Rotterdam and one in The Hague during the period of greatest starvation. The rates of abortion, stillbirth, neonatal death, malformation, and low birth weight were compared with those in 674 births in the same clinic in Rotterdam from 1938 to 1939 (Table 2-2). Note the incidence of malformations doubled and the incidence of neonatal death was more than three times higher among infants born during the last three months of 1945 than those born from 1938 through 1939.

Table 2-2
INFLUENCE OF HUNGER ON REPRODUCTIVE CASUALTY [503]

	<i>Births in Rotterdam 1938-1939 (674)</i>	<i>Births in Rotterdam (135) and The Hague (47) 10/1/45 to 12/31/45*</i>	<i>Percent Increase</i>
Per cent spontaneous abortions	1.67	8.33	399
Per cent stillbirths	3.50	4.09	17
Per cent neonatal deaths	1.55	4.94	219
Per cent malformations	1.36	2.95	117
Percent birth weight $<2,250$ g (4 lb., 15 oz.)	5.27	9.07	72

*Births likely to be conceived during a period of starvation.

Birth weight seemed to be an indicator of infant life and health. Of infants born in Rotterdam, the prevalence of birth weight under 2,250 g increased to 8.4 per cent during the last three months of 1945 from 5.3 per cent during 1938-1939. The prevalence in The Hague rose to 11.0 per cent.

There were instances in which, despite all of the unfavorable living conditions created by war, maternal and infant health actually improved. Because the British government upgraded the diets of pregnant women during World War II, stillbirths declined from 38 to 28 per 1,000 births from 1940 to 1945 [39], even though other living conditions during the same period deteriorated. Moreover, birth weights and growth rates increased. In contrast, Ireland, which sold much of its food to the United Kingdom, experienced a decline in birth weights during the same period.

A seemingly paradoxical near normal incidence of underweight births was also observed in both England and Germany during World War I [11]. Many investigators concluded falsely, from the lack of appreciable decline of birth weight in England from 1914 to 1918, that prenatal diet has little or no effect on the weight of the newborn. They failed to recognize that even though there was a general deterioration of living conditions during the war, marked

undernourishment among pregnant women in England and Germany was rare. Nevertheless, the theory that the fetus behaves like a parasite, i.e., that the fetus can adequately extract its nourishment from the mother's body regardless of her nutritional status, was still accepted on occasion as late as 1974 [60].

It is appropriate to deal here, at the outset, with a widely quoted study cited as showing *conclusively* that there are no detectable effects of severe but balanced nutritional deficiency during human pregnancy. That is, there are no effects on the physical or mental status of the offspring at maturity. This is the Stein-Susser analysis of the short-term but locally severe famine of western Holland in 1944 to 1945 [509,510], which contrasts with the analysis of the same events by Clement A. Smith [503]. In brief, Stein-Susser examined the tested capacities of army inductees born nineteen years earlier prior to, during, and after the period of famine. The evaluations were made on medical grounds as well as by intelligence tests.

The summary communication painted a bleak story [509], drawn from accounts of official rations. For example, in February 1945, the official ration was only 479 calories per day; in April 1945, the low point was 659 calories per day. These low values were apparently reached mainly in the cities of western Holland. Six weeks after the embargo imposed by German occupation forces, in November 1944, the deficiencies were severe; however, in many parts of the country, rations generally exceeded 1300 to 1500 calories per day.

Indeed, although not relying particularly on the immediate postwar survey by the Dutch government [75], Stein et al. placed additional data in their more extensive book [510], which confounds their conclusions offered in the earlier paper in *Science*. For example, they reveal there were other important sources of food, such as the Interchurch Bureau, the central kitchens, foraging parties, and the black market [510, p. 49]. These sources brought the values for February and April, the months of worst privation, up to 1290 and 1243 calories per day, respectively. They note in their book that distribution of food was further skewed by opportunity to procure and ability to pay.

Their presentation concluded that "social class/occupational category of father" was the prime determinant of effective fertility and successful pregnancy.

The official government report indicated the impact of the famine was felt by institutionalized and elderly persons, and by the urban poor, to telling effect [75].

Pasamanick has evaluated the occurrence of mental deficiency in these survivors [409]. He points out that no testing was done at or near birth, open-

ing the findings at maturity to the confounding effects of social causation. Nevertheless, congenital defects of the central nervous system, cerebral palsy, and severe mental deficiency were all found to be increased. These are the categories least susceptible to improvement by events of the intervening nineteen years. The rates of severe mental deficiency were 2.16 per 1,000 for the interval before the famine and 3.28 per 1,000 for offspring *in utero* first trimester during the hunger period [409], a highly significant difference.

Accordingly, even the brief interval of protein-calorie malnutrition experienced in Holland in 1944 to 1945, despite unevenness of distribution and the problems of reassessment long after the fact, can be shown by critical analysis to have had significant impact. Moreover, the full report by the most widely cited investigators of this problem substantiates the interrelation between maternal nutritional deprivation and subsequent injury to nervous system structure and function. It is appropriate, then, to develop in this book the very large body of information already available that supports this fundamental principle.

Compellingly, there is supportive information and data not often cited which confirms these general inferences. A seminal work on the effects of severe, ultimately fatal starvation, on humans is Myron Winick's compilation of research and clinical notes by physicians in the Warsaw ghetto during the most dreadful of the privations, in 1942: *Hunger disease; studies by the Jewish physicians on the Warsaw ghetto* [567]. This unique (and hopefully never repeated) record of starvation at these levels concentrates on the progressive pathophysiology of starvation. There are no quantitative data on pregnancy, which did occur, remarkably, but this extract says it all [567, p. 109]:

Adolescents entering puberty during the war remain generally and sexually infantile...In hunger disease, stunting of growth is equally distributed through the body and the extremities, but the face . . . appears old and can be described as "Gilford's progeria" or "Variot's senilismus." – Both sexes are sterile . . . In the *few cases* (emphasis supplied) in which babies are born, the survival rate was very low.

Food deprivation related to war is not limited to malign occupation. Some 8,500 kilometers by the great circle route east of Warsaw, and at the other end of World War II, profound effects were observed after the first year of the American occupation of Japan.

Gruenwald et al. [215] examined the records from three large Japanese obstetrical hospitals and found progressive birth weight increases for the twelve years after the base line of 1945-1946, a period of extreme civil privation and markedly low birth weights. As might be expected, in a nation mobilized for total war, there were substantially fewer births in 1945-1946. The three hospitals saw only 1365 births in 1945-1946. This rose to 6828 in

1957-1958 and to 7177 in 1963-1964. The decline in birth weights during the war was on the order of 200 grams, similar to the experience in Holland, but less than the profound 585 gram decrease seen in Leningrad. Upon entering Tokyo as the Supreme Commander for the Allied Powers, General MacArthur began an aggressive policy of rebuilding Japan, setting up kitchens and organizing the transfer of 3.5 million tons of American Army food. Facing bureaucratic hesitancy and grumbling in Washington, he cabled again: "Give me bread or give me bullets" [353]. It can only be imagined what would have happened to the health of pregnant Japanese women had it been necessary to reduce all of Japan to rubble to facilitate the planned invasion by massive military forces.

Outside the turmoil and duress of war and postwar reconstruction, the optimal food intake for pregnancy and the fetus remains illusive. A split in medical ranks between the biochemists and public health operatives in the field was well described by, and rather fostered by C. D. Williams [562]. She stated in 1962:

Actual food lack is not often the cause of malnutrition . . . To solve the problem of malnutrition we must study the causal factors. These cannot be solved in a laboratory by the biochemists.

She pointed out that not a few nutritional deficits are slow to take effect, requiring a long time to manifest clinically, with scurvy an excellent example. She cited Farmer in East Africa [166] who found 48 causes for 28 cases of kwashiorkor but only four for lack of food due to poverty. Her paper can be considered the high water mark of an exclusive cultural-social-habitual-economic model of reproductive casualty. Williams was correct, however, when she added:

Education for the experts is (just as) necessary . . . as for the indigenes . . . There is a certain gay insouciance among the medical profession in the advanced countries with respect to the problems of the less developed areas [562].

As will be made clear, the cause cannot be ascertained solely from study of the greater environment in which women are pregnant without the details of what pregnancy means biochemically and physiologically. While it is obvious, and true, that pregnant women eat foods, not amino acids or components of the citric acid (Krebs) cycle *per se*, the availability and efficacy of the chemical building blocks are involved in the outcome indispensably. Among the problems in interpretation of various clinical experiments with pregnancy nutrition is the way in which the essential ingredients are packaged *within* the food. Moreover, the situation is measurably more than a simplistic first order equation: more food for mother → a healthier infant. The reality is more indirect. These points will be discussed further in

Chapter 3 and beyond.

Starvation affects pregnant women differently from nonpregnant women [172]. The special qualities of the gestational response have implications for glucose metabolism [169,170,426] and for gestational diabetes mellitus [439].

Felig et al. [172] examined the effects of an 84-90 hour fast during weeks 16-20 of gestation just before scheduled pregnancy terminations. Nonpregnant controls showed two- to three-fold increases in plasma valine, leucine, isoleucine, and α -aminobutyrate; decreases were seen for alanine and glycine. Pregnant women in the postabsorptive state, by contrast, had falling levels of most amino acids. Exceptions were glycine, serine, and threonine, which rose substantially. Nonpregnant obese women showed changes similar to the pregnant women but only after a much longer time, beyond ten days (240 hours). Felig et al. pointed out that the amino acids which rose in both groups: valine, leucine, isoleucine, α -aminobutyrate, phenylalanine, and tyrosine, are those uniquely sensitive to change in endogenous insulin levels [170] and to the administration of exogenous insulin [428]. The findings support the concept that hyperaminoacidemia of starvation is due to hypoinsulinemia [168].

Caloric deprivation for 84-90 hours affects other aspects of metabolism as well (Table 2-3) [283]. The changes in glucose, β -hydroxybutyrate, acetooacetate, free fatty acids, and glycerol are dramatic in maternal blood, confirming starvation ketosis, but are dampened partially in amniotic fluid, as a marker for the fetal compartment. The glucose level fell by 37 per cent in maternal blood and 36.7 per cent in amniotic fluid, both significant decreases. The other four substances tested all rose with only amniotic fluid free fatty acids doing so marginally. Glycerol rose 59.5 per cent in maternal blood and 42.6 per cent in amniotic fluid.

Further details on the relation between amino acid deprivation and hypoinsulinemia will be covered in Chapter 5; diabetes mellitus was not discussed in detail in the first edition, only the association between hyperinsulinism and gestosis (preeclamptic toxemia [p. 84, first edition]).

Adaptation to low protein intake has importance when considering the effects of supplementation in different population groups. There is not just a single "normal" nutritional state of organisms. From the nutritional point of view, smallness is a favorable adaptation: small people need fewer calories and less maintenance protein. The initial response is a fall in urinary nitrogen excretion. There is not a single amino acid pool: each specific amino acid has its own compartment with fluxes dependent on where it is in the metabolic scheme [554].

Waterlow remarked on the frequent assumption that amino acid nitrogen can be treated the same whether it comes to the pool from food or from

Table 2-3
METABOLIC CHANGES AFTER 84-90 HOURS OF
CALORIC DEPRIVATION IN MID-PREGNANCY [283]

	Maternal blood			Amniotic fluid		
	Fed	Fasted	p	Fed	Fasted	p
Glucose mg/dl	75.1 ± 1.7	47.2 ± 2.0	<0.001	32.7 ± 2.0	20.7 ± 1.1	<0.001
β-hydroxybutyrate mmol/L	0.38 ± 0.04	3.79 ± 0.26	<0.001	0.11 ± 0.02	2.78 ± 0.24	<0.001
Acetoacetate mmol/L	0.08 ± 0.01	0.66 ± 0.08	<0.001	0.06 ± 0.01	0.61 ± 0.07	<0.001
Free fatty acids μEq/L	959.5 ± 102.8	1563.5 ± 91.8	<0.001	76.3 ± 17.6	87.2 ± 21.2	ns
Glycerol μmol/L	173.8 ± 38.2	277.2 ± 38.5	<0.1	127.1 ± 17.6	181.3 ± 36.4	<0.025

catabolism [554]. This is a not self-evident principle; there is no evidence for it. Intra-gastric synthetic and catabolic rates were higher than those obtained intravenously. Low protein intake results in a much lower ¹⁵N excretion fraction, 3.4 per cent against 24.3 per cent. Labelled arginine as tracer showed hepatic protein resynthesis rising from 50 per cent to 70 per cent when protein intake was low. Waterlow suggested an endocrine:metabolic control mechanism but did not investigate further this possibility.

Indeed, even short periods of total food lack have an effect. The 24-hour fast of the religious holiday, the Day of Atonement, Yom Kippur, has the obstetric effect of doubling the number of near term births (*per diem* rate) from the cohort of women in late pregnancy [276]. This phenomenon has been shown, in rhesus monkeys, to have a hormonal basis, namely: lowered maternal blood glucose results in increased maternal arterial prostaglandins which stimulate nocturnal uterine contractions [37]. Fuel metabolism in the pregnancy is characterized by phenomena called "facilitated metabolism" and "accelerated starvation" [72,73,184]. The mechanisms are adjustments to metabolism which include insulin resistance and increased insulin response to a glucose load. In the fed state, both adjustments will shunt ingested carbohydrate to the fetus and ingested lipid to adipose tissue. In the fasting state, decreased gluconeogenesis leads to hypoglycemia, increased lipolysis, and to ketogenesis. These changes are most likely to be mediated by placental lactogen (see p. 218) and progesterone [198] and by the presence of increased plasma triglycerides and free fatty acids [320]. This is thought to produce a postreceptor decrease in insulin action most prominent in skeletal

muscle [79,538], along with decreased protein catabolism, decreased hepatic gluconeogenesis, and increased lipid catabolism [73]. The precise mechanisms involved are a matter of conjecture [398].

The anabolic nature of pregnancy imposes several obligatory extra energy costs [425], which may precondition a pregnancy to negative consequences of the special metabolism. Marginally nourished women conserve energy by suppression of metabolic activity (rate) and gaining little fat. Birth weight is directly proportional to maternal gain above 7.0 kg (an exception is Gambia, with a mean gain of 6.4 kg, and about the same birth weight as those with modestly higher maternal gains). Poppitt et al. found gain to be more predictive than per cent prepregnancy fatness [425]. Birth weight as per cent of maternal weight gain was inversely proportional to the amount of gain. Neonatal weight was fairly constant at 15.0-17.0 per cent of maternal weight gain [425]. This argues for limits to maternal:fetal efficacy, without indicating just where that might occur, or where the several levels of control occur, if more than one.

The same conclusion is strongly indicated in the 1981 report by Rosso [460]. Rosso considered maternal weight gain versus birth weight across three ranges of "ideal" prepregnancy weight. When prepregnancy weight was more than 20 per cent over ideal, there was no effect on birth weight irrespective of maternal weight gain. Similarly, none or very few low birth weight infants were delivered by women with higher than ideal prepregnancy weight, no matter how much weight they gained. Finally, immediate post-partum weight had a relationship to the birth weight of the infant only up to 110 per cent of ideal. In other words, transfer of nutrient for protein synthesis and growth and maturation of the fetus can be influenced only up to a point [460]. This has unmistakable implications for programs which encourage unlimited weight gain as well as providing some insight into the results of more limited nutritional supplementation. Rosso also demonstrated that the maximal fetal weight effect required the gain of at least 10 kilograms in underweight mothers. The mean birth weight for such women, from a study of 254 pregnancies gaining less than 6.0 kilograms, was 2748 grams. The mean birth weight for those gaining 10.0 kilograms or more was 3453 grams, an average increase of 705 grams, or 25.7 per cent, a highly efficacious result.

The opposite problem is that of the obese gravida, one ≥ 20 percent beyond the Metropolitan Life Insurance Company's standard weight for height for women [113]. Marked caloric restriction is potentially very harmful. The proper approach is very close supervision by an obstetrical nutritionist directed at the correction of eating habits while providing sufficient food intake for a smooth and progressive gain of 10.7 kilograms (24

pounds); micronutrient supplementation is requisite, especially for iron and folic acid.

A critical aspect of dysnutrition in pregnancy is iron deficiency anemia [547]. This is the single most prevalent nutritional disorder worldwide. Over 2 billion persons are iron deficient and 1.2 billion have iron deficiency anemia. One-third of the developing world and 11 per cent of the industrialized world have iron deficiency. Some 60 per cent of pregnant women are anemic world wide; the prevalence is less in the industrial countries, ranging between 9-14 per cent.

The prevailing nonchalance noted forcefully in the first edition of this book is still with us. There is a tendency to look to ultrasophisticated analytic techniques to bring enlightenment from study design matrices crowded with data. A straightforward assessment in a limited but stable population, one seeking direct answers to a well-defined question, often does much better. One example of this is the report of Delgado, Martorell, and Klein from rural Guatemala [129]. The study was limited to the relation of maternal nutritional status and infant food supplementation on the duration of puerperal amenorrhea, the interval of subsequent menstruation, and the start of the next pregnancy. A significant negative association was found amongst these factors. The women were of small stature (mean weight = 50 kg [112 pounds]). The data suggested the limiting factor was calories, not protein at 45 grams/day during pregnancy and at 61 grams/day during lactation. Longer-term puerperal amenorrhea was associated with a shortened menstrual interval and protracted lactation was associated with a longer menstrual interval. The study ruled out nutritional status and nutrient intake as regulatory factors for the length of the intergestational menstrual interval [129]. Nutrient intake is a factor in the *volume* of breast milk produced [158].

These cautions notwithstanding, sometimes it is vital to take a different look at the problem. Pelletier et al. found compelling evidence from pattern analysis to show infant mortality increases exponentially with declining weight for age [417]. The effect was determined to be consistent over six major studies. No threshold effect was identified. This confirms that mild to moderate malnutrition is definitely associated with increased risk of mortality. Mortality depends on the rate of morbidity and the contribution of morbidity varies according to prevalence of malnutrition. The basic principle here is that the usual marker or proxy for malnutrition, specifically infant mortality, is only indirectly valid if at all and the dynamics of the intermediate factor or factors and conditions will require more complete understanding of the biology of the matter before an ideal solution can be suggested, if there is one. Williams could not see this far ahead, as any of us might have had equal trouble doing. We will have to make use of such

reasonable information which experience and some investigations have wrought.

Chapter 3

THE INFLUENCE OF PRENATAL NUTRITION ON MATERNAL AND INFANT HEALTH

THE CAUSAL RELATIONSHIP between maternal malnutrition and developmental disabilities is documented in various prospective nutritional studies, some of which are reviewed here. The questionable ethics of withholding from a group of pregnant women nutrients and/or calories, deficiencies of which can cause permanent neurological impairment in their offspring, preclude the opportunity to study prospectively the effects of dietary deprivation as thoroughly as has been done in numerous animal studies. Unfortunately, the application of animal studies to humans has been discounted unjustifiably often. This failure to recognize the implications of animal studies, coupled with the refusal to accept the validity of various prospective and retrospective nutritional studies on the effects of malnutrition on reproductive casualty, has led to numerous additional studies – many of them recently conducted in, or sponsored by the United States [210,592] – in which pregnant women are indirectly denied adequate nourishment.

BASIC ANIMAL NUTRITIONAL RESEARCH

Nutritional research in laboratory animals overcomes the most serious problem associated with clinical studies, often widely uncontrolled circumstances [138]. When viewed by this perspective the procedural dynamic becomes: (1) description of findings or operational principles in animal models, and then (2) determining their applicability to the human condition. As a rule, whether the animal work and human studies agree or not, the point is to find out why they agree, if they do, or why not, if they don't. The

great differences in growth rates and gestational time between small laboratory animals and humans have to be taken into account, but they do not automatically rule out applicability of the conclusions from specific studies or opportunities. The past thirty years have seen important nutritional work in animals of relevance to human pregnancy. For example, Dobbing and Sands have shown that developmental timetables for the brain were unaffected by undernutrition, though the extent of development often was [138,140,141]. This was confirmed specifically by West and Kemper [557]. Low protein diet reduced the thickness of the rat visual cortex by 11 per cent, the molecular layer of the cerebellum by 16 per cent, and the length of basket cell oblique branches by 16 per cent as well. Experimental animals were fed 8 per cent casein, while controls received an isocaloric diet with 25 per cent casein. Synaptic spine density decreased with smaller dendritic processes for some but not all dendrites. These are functionally important details [95,273].

The brain is both anatomically and developmentally complex. This includes the neuromuscular junctions [33]. As such, significant periods and events for one area may differ from the requirements for another. Hippocampal granule cells are acquired postnatally in the main and are a test of the delayed effect of prenatal protein deprivation (such as half rations from day 6 onward). Lewis et al. [323] found overall cell cycle time, S-phase, and G₂-phase to take longer, while the G₁-phase was dramatically shortened, at 1, 6, and 12 days. The architectural consequence of this, at 12 days, was a thinner granular layer: $66.5 \pm 3.8 \mu\text{m}$ versus $77.8 \pm 7.1 \mu\text{m}$, with fewer cells [323].

Multiple quantitative measurements of the central nervous system under controlled dietary conditions are only possible in animal models, as was shown compellingly by Manocha et al. in primates [354-356] and in rodents by Morgane et al. [386] and Noback and Eisenman [403]. The latter was a

Table 3-1
BODY AND BRAIN WEIGHTS AND THICKNESS OF
SELECTED REGIONS OF THE CENTRAL NERVOUS SYSTEM [403]

	<i>Control</i>	<i>Undernourished</i>	<i>p</i>
Body weight	$34.58 \pm 4.96 \text{ g}$	16.00 ± 1.07	<0.001
Brain weight	$1.31 \pm 0.026 \text{ g}$	1.10 ± 0.051	<0.001
Thickness			
Dentate gyrus	$297.5 \pm 3.8 \mu\text{m}$	286.25 ± 2.85	<0.05
Hippocampus	595.0 ± 4.52	582.5 ± 4.098	<0.05
Parietal	1392.5 ± 9.29	1290.0 ± 4.52	<0.001
Paravermis	394.0 ± 2.85	285.5 ± 3.47	<0.001

Values are means \pm standard errors of the mean (S.E.M.)

postnatal study on rat pups from dams fed a low protein, calorie restricted diet; assessments were on postnatal day 21 (Table 3-1).

In addition to these important findings, the number of spines differed significantly only for pyramidal cells, hippocampus, and the parietal neocortex; granule cells of the dentate nucleus and cerebellar purkinje cells were not affected ($p>0.05$) [403].

Functional effects of similar prenatal deprivation studies have been done less often, because, one presumes, of the greater technical requirements.

Bronzino and others have examined the close relationship between kindling (behavior modification in response to invariant stimuli [188], sometimes viewed as epileptogenic [65]), and prenatal protein malnutrition [65–68], with seizures as a result. Rodents have been shown to have changes in seizure susceptibility under the influence of developmental protein malnutrition [511]. The clinical parallel is discussed on page 169.

One must keep in mind, in such experimental work, a prenatal deficiency may manifest as an exaggerated functional response later, through the process of upregulation. Chen et al. [95] observed that serotonin receptor and transporter binding and affinity were normal in male rats from dams kept at 6 per cent casein but reared after birth by dams kept on a control diet of 25 per cent casein. Despite this, there was a two-fold greater basal serotonin efflux from deprived pups over a 20-minute test period.

Changes in brain observed in the early postnatal period after induction prenatally by protein deficient diets will persist for experimentally long periods of time [132,133]. Microarchitectural changes present at 15 days postnatal were found to persist for 220 days: reduced cell size, a decreased number of synaptic spines along the entire dendrite, and reduced complexity of dendritic branching in the outer two-thirds of the molecular layer. These differences were all significant on measurement grounds [132,133].

Similar conditions greatly reduce the amount and rate of myelinization of the white matter of the brain, leading to reductions in brain weight as high as 60 per cent at 20 days and 70 per cent at 60 days [298]. Comparable evidence for irreversible functional effects have been found in clinical studies [246,514].

PROSPECTIVE NONINTERVENTIONAL STUDIES IN HUMANS

A notable prospective scientific study in 1943 of 216 births at the Harvard University Department of Public Health documented the relationship between nutrition during the last two trimesters of pregnancy and subsequent birth weight and infant health [76-78]. Thorough dietary histories were taken of all the pregnant women, many of whom were of middle income

status; the first history was taken at the initial prenatal visit. Although a control group was not used for comparison, the data collected are revealing enough to make a control group unnecessary through category stratification.

From the dietary information acquired by nutritionists, the women were classified into five different groups depending upon their intake of various nutrients and calories [76,78]. The five groups, as defined, were distributed in a nearly symmetric manner (Table 3-2).

Table 3-2
DIETARY RATINGS BY NUTRITIONISTS
IN THE STUDIES BY BURKE [76-78]

Category	Number*	Per cent	Rated as undernourished
Good to excellent	31	14.35	No
Fair to good	36	16.67	No
Fair only	63	29.17	No
Poor to fair	50	23.15	Yes
Very poor to poor	36	16.67	Yes

*These data laden papers of Burke, et al., are representative of the unfortunate practice of reporting percentages, not original raw data, requisite for statistical calculations. The number of cases are from incomplete comments in one text with recalculation of the rest [76]. The percentages given above differ slightly from those in the cited papers and the first edition of this book.

As the right-hand column emphasizes, 40 per cent of the women were found to be undernourished. There was no dietary intervention at any time in the study. These were entirely descriptive reports.

The level of maternal protein intake, which paralleled the general dietary intake, was significantly related to the length and weight of the child at birth. Infant size at birth increased with each increment of dietary protein [77]. Importantly, none of the infants born to women who had an intake of at least 80 g of protein weighed under 2,724 grams; the median birth weight of these infants was 3,856 grams. In contrast, 47 per cent of infants born to women on very poor diets (under 45 g of protein) were of low birth weight. Among these births, the median birth weight was about 2,500 grams. The author claimed that for every additional 10 g of dietary protein per day, up to 85 to 100 grams, the birth weight would be increased 240 grams. Maternal height had practically no influence on infant length when protein intake was taken into consideration. The correlation between birth length and protein was 0.80 ± 0.03 ; with the effect of maternal height removed, the correlation was 0.78 ± 0.03 [77]. These high correlations indicate the probability that maternal protein intake and birth length are unrelated is less than one in a billion.

Equally compelling was the demonstrable effect of prenatal nutrition on neonatal health. Neither the obstetricians evaluating the infants at birth nor

the pediatricians who examined them within the first two days of life were aware of the nutritional status of any of the mothers. So the examinations of the infants would be relatively unbiased with respect to nutrition, all the professional examinations were done independently.

Superior physical condition was defined as no physical abnormalities detectable from birth to one or two weeks of age; good health was defined as one or two minor physical problems; fair condition was defined as more than two physical problems, but less than the final category; poor was defined as having congenital malformations, otherwise poor physical development, or birth weight below 2270 grams. The distribution of these findings was revealing (Table 3-3).

Table 3-3
PHYSICAL CONDITION AND STATE OF HEALTH
BY PHYSICIAN ASSESSMENT [76-78]

<i>Category</i>	<i>Number</i>	<i>Per cent</i>
Superior	23	10.6
Good	84	38.9
Fair	76	35.2
Poor or died	33	15.3

Besides demonstrating the profound effect of maternal nutrition on infant health, this prospective study strengthened the concept that birth weight is an accurate indicator of infant health. Birth weight was remarkably associated with the pediatric rating. The average birth weight of superior infants was 3,685 grams; that of infants in good health, 3,515 grams; and that of the thirty three infants rated as poor, 2,693 grams. The interrelation of these factors is shown in Table 3-4.

Birth length showed a similar relationship to the pediatric rating but was not as significantly related as birth weight.

Birth weight, which is influenced by nutrition more than any other

Table 3-4
RELATION OF PRENATAL NUTRITION AND
BIRTH WEIGHT TO NEONATAL HEALTH [78]

	<i>Neonatal rating of infants</i>			
	<i>Superior</i>	<i>Good</i>	<i>Fair</i>	<i>Poor</i>
Number of infants	23	84	76	33
Mean birth weight (grams)	3685	3515	3232	2693
Good or excellent prenatal diet	56%	19%	1%	3%
Poor or very poor prenatal diet	9%	2%	12%	79%

environmental factor, was shown to be directly related to prenatal diet. The average birth weight of infants delivered by women on excellent or good diets was 3,853 grams compared to 3,371 grams among women on fair diets, i.e., the 149 women whose diets were classified as fair to good, fair, or fair to poor [78]. Infants born to women who had poor to very poor dietary intake had an average birth weight of 2,635 grams – 1,218 grams less than the average weight for infants of the best fed mothers (Table 3-5).

Table 3-5
RELATION OF BIRTH WEIGHT AND
INFANT HEALTH TO PRENATAL NUTRITION [78]

	<i>Prenatal diet</i>		
	<i>Excellent or good</i>	<i>Fair</i>	<i>Poor to very poor</i>
Number of infants	31	149	36
Average birth weight	3856 g	3374 g	2637 g
Pediatric rating of superior or good	29 (94%)	76 (51%)	3 (8%)
Pediatric rating of poor	1 (3%)	7 (5%)	24 (67%)

See the footnote for Table 3-2 which applies here.

Thirty-three infants died, weighed under 2,270 grams at birth, or were in poor health. Seventy-nine per cent of these were born to women who had been on poor to very poor diets; only 3 per cent of this group were born to women on good or excellent diets [76,78]. In contrast, among the twenty-three infants in superior health, 56 per cent of the mothers were on good or excellent diets, whereas only 9 per cent had poor to very poor diets (Table 3-4).

Sixty-seven per cent of the infants born to women on poor to very poor diets were stillborn, died within three days of life, weighed under 2,270 grams at birth, were functionally immature, or had congenital defects [76,78]. Only 8 per cent of the infants born to women on such diets were classified as superior or good condition. In contrast, 94 per cent of the infants born to women on good or excellent diets were in superior or good health, whereas only 3 per cent were in poor health (Table 3-5).

Burke's prospective nutritional study had the advantage that dietary and neonatal assessments were not known to the other arm of the investigation. The study was noninterventional so the analytic phrase *double blind(ed)* is not appropriate in this situation.* The study design was the procedural equiva-

*The standard meaning of a double blinded study is neither the person actually supplying a treatment (usually a medication) nor the subject receiving it knows whether it is the material undergoing testing or a fake medicine (placebo).

lent of a double blind trial. The work in these three papers shows prenatal nutrition to affect infant health profoundly and beyond dispute [76-78]. Burke's data show that the *probability that prenatal nutrition is unrelated to infant health is less than one in a billion.*

Dieckmann et al. strongly confirmed Burke's findings of the obvious relationship between maternal protein intake and pediatric ratings of infants ($p = 0.0001$) [135]. There were 612 carefully supervised pregnancies, especially with regard to maternal nutrition. The frequency of low birth weight was 3.3 per cent; the low birth weight incidence for women from similar socio-economic backgrounds but without intense nutritional management was 6.3

Table 3-6
RELATION BETWEEN DIETARY PROTEIN, INFANT HEALTH,
AND MISCARRIAGES (FIRST TRIMESTER LOSS) [135]

Maternal daily protein intake	Number of		Per cent first trimester loss	Per cent infants in superior health
	Women	Miscarriage		
<55 grams	74	6	8.11	35.7
55-70	178	7	3.93	41.6
71-85	238	3	1.26	63.9
>85	106	0	0.00	72.9

per cent, a statistically significant difference. Table 3-6 shows also that miscarriage was significantly associated with low protein intake ($p < 0.002$).

Dieckmann's study was not strictly prospective in the sense of just simple data collection. The diet program included loaning the mothers a dietetics scale for weighing food at home. As results were tabulated, some effects of instruction about foods seemed to take hold and the protein intake rose slightly. At the start, 60 per cent of the mothers consumed ≤ 70 grams protein per day but by the end of the study, this had fallen to 42 per cent. This change was accounted for in the final conclusions. Pediatric rating of the infants was completely independent from the rest of the program; those findings were brought in and analyzed only at the conclusion of the work.

Not related to nutrition, as far as is known presently, and not extended observationally to late pregnancy disturbances, is the curious report of multiple spontaneous abortions possibly related to high nitrate content of well water [617].

EFFECT OF NUTRITION ON BIRTH WEIGHT

The relationship between nutrition and birth weight has been documented for decades. A study of maternal nutritional status of 364 infants in the Philippines in the 1920s showed a striking association with birth weight [7].

Of the 364 infants studied, obstetricians rated maternal diet into three categories in 168 cases; interns and clinical clerks similarly rated diets of the other 196. As nutritional status worsened, both the maximum and average birth weight declined, with a difference of 500 grams in the average. Prevalences of low birth weight, listed in Table 3-7, were significantly lower among the better fed women. The women on the worst diets were more than ten times as likely to give birth to a low birth weight infant as the best fed women.

Table 3-7

RELATION BETWEEN PRENATAL NUTRITION AND BIRTH WEIGHT [7]

<i>Nutritional status in pregnancy</i>	<i>Number of women</i>	<i>Per cent low birth weight</i>	<i>Maximum birth weight</i>	<i>Significance of difference in low birth weight*</i>
Good	63	3.2	4,400 g	0.005
Fair	272	11.0	4,300	—
Poor	29	31.0	3,340	0.005

*Fair nutritional status as baseline; $\chi^2 = 15.2517$, 2 x 3 table, $p = 0.0005$.

Even among women in extreme nutritional circumstances, the use of sound nutritional guidance lowers the risk of low birth weight, including total parenteral nutrition (TPN) during pregnancy [315]. In a prospective study of four pregnant women after jejunointestinal bypass surgery, Taylor and O'Leary compared the birth weights of the children born afterwards to infants born prior to the operation [521]. The mothers lost 15 to 55 per cent body weight. Two women were given multivitamins, iron supplements, and instructions to follow a high protein diet (100 to 150 g daily). The birth weights of these infants were somewhat but not significantly higher than for two other women given the supplements but told only to follow a regular diet (more substantial than diets usually given to obese women [53,286]). The average birth weight of children born after bypass surgery and supplementation (3,138 grams) approached that of four births prior to the operation (3,192 grams). At birth, two of the children weighed more than their siblings and two weighed less. Most importantly, none of the four study group children were underweight at birth. These are the best results so far reported for this clinical problem.

Taylor and O'Leary reviewed nine earlier cases of childbirth after jejunointestinal bypass. They found low birth weight occurred in 67 per cent, a significantly higher frequency ($p < 0.025$). It is noteworthy, for all six examples of low birth weight, that the mothers either lost or gained very little weight during pregnancy. The nine cases demonstrate a nutrient depleting effect of jejunointestinal surgery. The average birth weight of children born to the

six women with at least one child prior to surgery was 3,365 grams; in contrast, the average birth weight of four children born to the same women after surgery was 2,585 grams, a difference of 780 grams, considerably less than siblings born before jejunoileal bypass ($p<0.05$). In all cases, the child born after the operation was the lowest birth weight child. The importance of these unusual cases comes from the four infants whose mothers received nutritional counselling and supplementation during the pregnancies. The mean decrease in birth weight for them was only 54 grams. This difference in outcome confirms the value of special nutrition counselling and management which added, on average, 726 grams of fetal growth!

There have been several somewhat similar cases published since 1979, four with useful details [69,233,336,351,539]. A striking clinical history is that of LoIudice and Chandrakaar [336]. A 27-year-old had jejunoileal bypass two years before the 25th week of pregnancy. In the year after surgery, she went from 160.7 kg (360 pounds) to 69.6 kg (156 pounds) where her weight stabilized. Her presenting symptoms were intractable nausea, emesis, and diarrhea of more than ten watery stools per day. She gained 6.25 kilos from the 18th to the 25th week and was then placed on TPN. Delivery at 40 weeks, after three hours of spontaneous labor, yielded a 2640 g female infant, Apgars 9 and 10. Follow-up at one year was entirely within normal limits. The first pregnancy was unrelated: a preterm delivery, 28 weeks, Potter syndrome, birth weight of 1100 grams.

Hatjis and Meis [233] found that 1300 kcal per day was needed for the patient to gain appropriate weight. Nevertheless, at delivery at 36 weeks, the male infant weighed 2380 g. Another woman with a complex history of Crohn disease for six years was treated with TPN institutionally at first but was maintained on home TPN[69,539]. Resting energy expenditure of 6 MJ (1450 kcal) was determined and her daily allotment was raised to 10 MJ (2400 kcal). Normal vaginal birth at 37 weeks resulted in a 2620 gram female infant in good condition. Main et al. [351] maintained a patient with Crohn disease at first by nasogastric feedings for five weeks. Unfortunately she lost weight and the serum albumin level fell below 2.5 gm/dl. Therapy was switched to TPN set at 11.8 MJ (2800 kcal) with various micronutrient supplements in the 26th week of gestation. She then gained weight progressively (circa 10 kg), the serum albumin and transferrin rose, and a 2400 gram female was delivered at 36 weeks by section. These cases, taken together, suggest a possible limit on fetal growth despite seemingly sufficient maternal caloric TPN (Table 3-8).

Birth weight does not correlate with final levels of insulin growth factor-I [245], but does when viewed cumulatively, in fact, a plot (Figure 5-7) of cumulative IGF-I is linear against birth weight.

Table 3-8
BIRTH WEIGHTS AND GESTATIONAL AGE FOLLOWING
PROLONGED TOTAL PARENTERAL NUTRITION

<i>Author</i>	<i>Duration TPN</i>	<i>Calories</i>	<i>Gestational age</i>	<i>Birth weight</i>	<i>Sex</i>
Hatjis [233]	20 days	3800	36 wk	2380	M
Tresadern [539]	12 weeks	2400	37	2620	F
Loludice [336]	3 weeks	n.a.	40	2640	F
Main [351]	10 weeks	2800	36	2400	F

THE MONTREAL DIET DISPENSARY NUTRITIONAL PROGRAM

An individualized nutrition intervention program at the Montreal Diet Dispensary confirmed and expanded on previous reports which linked prenatal nutrition to birth weight and survival [242,431,592]. Seventeen hundred thirty-six women from the lowest income group in Montreal, many of whom had high rates of previous reproductive casualty, comprised the study. Two-thirds of the women in the study, which took place between 1963 and 1972, had completed no more than five years of primary education. The 1,246 women (72% of the total) who were below the 1971 Canadian poverty level (\$3,312 annual income for a family of four) received food supplementation in the form of milk, eggs, and oranges. All 1,736 women were provided extensive nutritional education and were given multivitamin supplements. The average length of service was eighteen weeks. Remarkably, 95 per cent of the women in this wholly voluntary study completed it.

The nutritional education and supplementation program was set up and implemented for the sole purpose of supplying pregnant women with as much as possible of their optimum nutritional requirements. The objective for their offspring was to be mentally and physically healthy. Collection and analysis of data were of secondary importance. Since women registered for the program at different stages during pregnancy, positive results were presumed to be biased in favor of those who enrolled early.

Extra nutritional requirements were examined for stress, underweight status, and previous undernourishment. The staff of the Montreal Diet Dispensary tried to have women satisfy these additional requirements through food supplementation and/or dietary education on an individual basis. For all women, the average daily protein intake was increased from 68 to 101 g; the average caloric intake was increased from 2,249 to 2,778 kcal per day.

Analysis of the data showed that diet dispensary staff underestimated protein and caloric requirements (especially for underweight women and those under stress), even though they insured women a greater nutritional intake than what was then recommended by the Canadian Council on Nutrition and the National Academy of Science/National Research Council's Recommended Daily Allowances for pregnant women [242]. Generally, as caloric and protein intakes increased, birth weight increased. There was an especially high correlation, even among women consuming above 127 per cent of their calculated protein requirements, between the per cent of the daily protein requirement consumed and birth weight. The average birth weight of infants from women whose protein intake was 84 per cent or less of their calculated requirements was 3,235 g; the birth weight of infants from women obtaining 115 per cent or more of the calculated need was 3,447 g, a difference of 212 grams, or 6.55 per cent increase above the mean achieved by the low protein intake women.

Even though the duration of nutrition intervention was less than half the average pregnancy, the success of Higgins' nutrition program was shown by sharp increases in birth weight and head circumference and a decline in mortality. The prevalence of low birth weight was 6.87 per cent, which, as a result of the large number of women registering late in pregnancy, is higher than found in some other studies [61,211-213] but much lower than the 9.04 per cent among other public patients not in the program but delivered at the same hospital ($p<0.005$) [242,431]. Remarkably, the low birth weight incidence of the women who were under age eighteen, a group with a contemporaneous incidence of about 10 per cent low birth weight in the United States, was just 3.3 per cent.

Some women participated only once in the special program. When the result of their participation was compared to the outcome of earlier or later pregnancies, or both, the program infant weighed significantly more than any sibling ($p<0.01$) [242,431]. A review of the case history of a particular 29-year-old woman unequivocally demonstrates the value of nutritional education and supplementation [242]. Figure 3-1 reveals the birth weight record of her children, all of whom were delivered at the same hospital. The mother was serviced by the Montreal Diet Dispensary (MDD) only during her last three pregnancies.

The third child died at the age of one month. A physical and mental assessment of the other children determined that *all* of the first seven surviving children are neurologically impaired, whereas all of the three youngest children are healthy.

Note that, at birth, the smallest child of the diet dispensary births weighed 489 grams more than the largest of the previous eight children. There is less

than one chance in a billion that such a major difference between the birth weights of the first eight children and those of the last three was caused strictly by chance.

For each of the woman's last three pregnancies, the cost to the diet

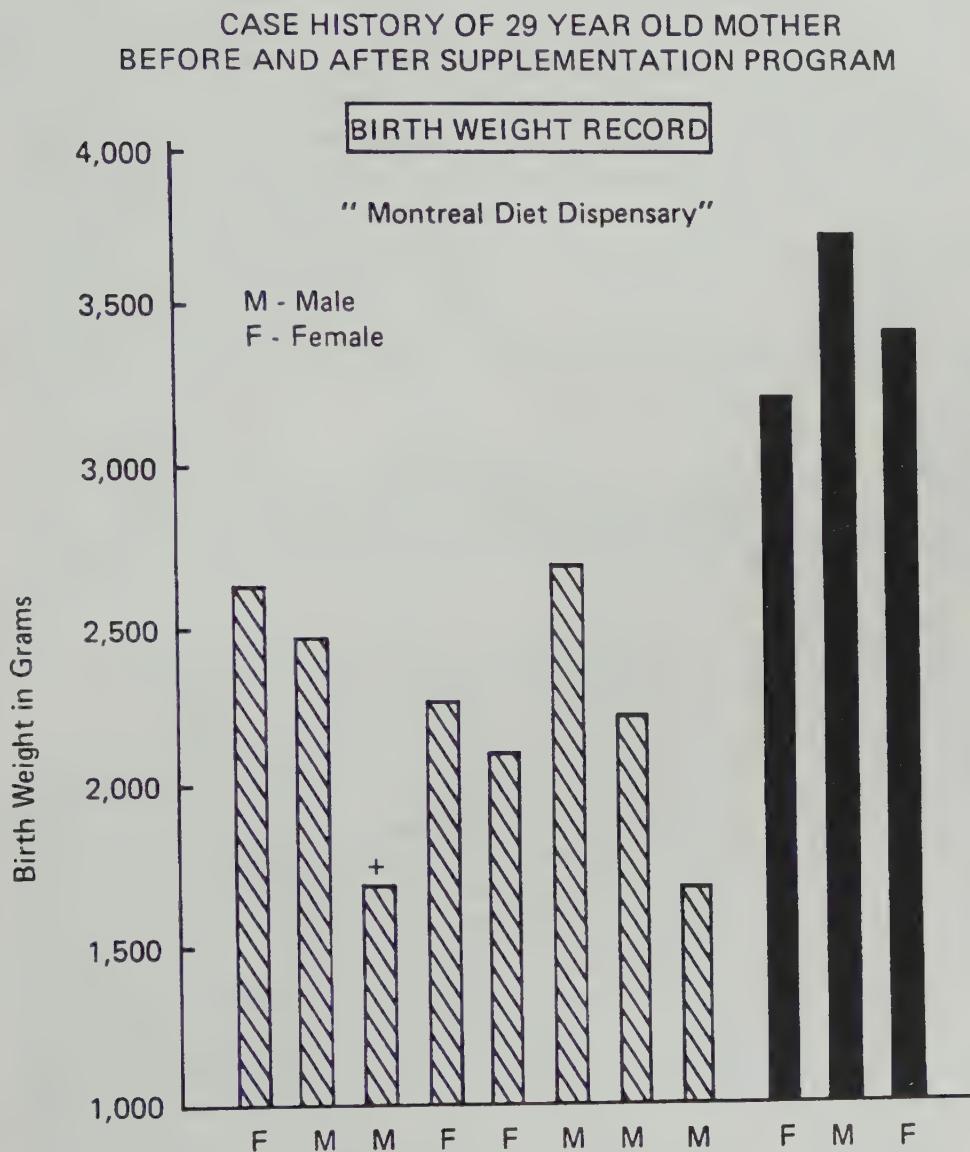


Figure 3-1. Courtesy of A.C. Higgins: Montreal Diet Dispensary Study, Nutritional supplementation and the outcome of pregnancy. Proceedings of a workshop, National Academy of Sciences, National Research Council's Committee on Maternal Nutrition, 1973.

dispensary for providing nutritional education and food supplementation was \$125 (1971 Canadian dollars) — a very small fraction of the public and private cost for providing services during the lifetime of a child with neurological impairment. By 1979, more than \$300,000 of public funds had been expended for rehabilitative care for the woman's first seven surviving children. None of her last three children required any special services.

The low birth weight rate in the Montreal Diet Dispensary nutrition program is higher than that observed in other sound maternal nutrition programs primarily because, as mentioned previously, the data include a large number of malnourished women who registered with the diet dispensary during the last few weeks of pregnancy. Some women received less than one week of food supplementation and/or nutritional education before they delivered. Generally, birth weight increased as length of service with the diet dispensary increased [242]. As shown in Table 3-9, women who participated in the program for at least twenty-one weeks had a much lower rate of low birth weight than women who were serviced for less than twelve weeks ($p<0.001$).

Table 3-9
LOW BIRTH WEIGHT AND DURATION OF PARTICIPATION
IN THE MONTREAL DIET DISPENSARY PROGRAM [242,431]

<i>Weeks of nutrition counseling</i>	<i>Live births</i>	<i>Low birth weight infants</i>	<i>Per cent low birth weight</i>
1-12	519	51	9.83
13-20	499	39	7.82
21+	713	29	4.07
Total	1731	119	6.97

Another probable explanation of the frequency of low birth weight in the MDD study (as compared with other studies which have been reviewed) is that approximately 20 per cent of the women in the study were also prescribed diuretics and placed on low salt, low calorie diets by the hospital physicians despite Higgins's very strong opposition. These practices were subsequently acknowledged to be hazardous prenatal regimens [242,584]. As will be elucidated later, the use of low salt, low calorie diets and diuretics, singularly or in combination, reduces birth weight.

Higgins showed that head circumference and birth weight are directly related [242,431]. For every centimeter increment in head circumference, the average birth weight increased. When cases of macrocephaly are excluded, head circumference can be considered a crude measure of intelligence. For

infants with a head circumference at birth of under 33.0 cm, the average birth weight was 2,553 grams. Among infants with a head circumference of at least 34.0 but less than 35.0 cm, the mean birth weight was 3,258 grams. The mean birth weight of infants with a head circumference of at least 37.0 cm was 3,956 grams.

The total perinatal death rate (fetal deaths of at least 28 weeks gestation, stillbirths, and neonatal deaths per 1,000 live births plus stillbirths) was 14.33/1000 in the diet dispensary program, at least 19.18/1000 among other public patients in the same hospital (no data were provided on neonatal deaths after seven days), and 26.65/1000 in Canada overall at the time of her report [91,159]. These differences in perinatal loss are highly significant ($p < 10^{-5}$). Even when birth weight was adjusted for other variables, it was significantly associated with length of dietary service, indicating that birth weights likely would have been higher had women registered earlier in their pregnancies [242,431]. It is significant that birth weight was not associated with length of nondietary service among other public patients not participating in the program who were at the same hospital. The average birth weight for the 521 women who received food supplements and were in the program for at least twenty-one weeks was 3,381 g, approximately 100 g more than the average birth weight for women seeing private obstetricians at the same hospital. The average birth weight among other public patients at the same hospital was 3,127 g, 254 grams less than the 521 women in the diet dispensary group.

PROSPECTIVE INTERVENTIONAL EFFECTS ON MATERNAL NUTRITION

Even a shorter period of food supplementation than provided at the Montreal Diet Dispensary can result in a substantial increase in birth weight. Iyenger confirmed the results of a previous study which showed that supplemented diets consisting of 2,300 calories and 85 g of protein per day during the last four weeks of pregnancy increased birth weights 200 to 300 grams [257,545].

Iyenger hospitalized 25 women during their last four weeks of gestation and increased their daily caloric intake from 1,400 to 2,100 [256]. The average protein intake had been a low 40 grams daily, all from vegetable sources. Thirteen of the 25 women were provided a diet consisting of 60 g of protein of which 20 g were animal protein. Twelve others received 90 grams of protein per day, which included 20 g of animal and 30 g of dairy protein. This can be achieved from 2.33 ounces of poultry or lean beef or 3 eggs and 1 quart of milk or 4 ounces of cheese. All 25 women received iron and

multivitamin tablets. The maternal and neonatal (cord) serum albumin concentration and birth weights were compared with the respective values of yet another 26 women of the same economic class who did not participate in the study.

The average birth weight for all 25 women given supplements of either kind was 3,028 g compared with 2,704 g among the control group, a difference of 324 grams. The probability that birth weight was not affected by food supplementation is infinitesimally small.

Higher serum albumin levels were found in the group given the food supplements (2.72 g/dl in both the 60 and 90 g protein groups) than in the control group (2.58 g/dl). The average serum albumin level among the women on a 90 g protein diet was significantly higher than that of the controls ($p < 0.0001$).

Iyenger concluded the additional 30 g of protein did not further increase maternal serum albumin concentration or birth weight because both groups received isocaloric diets [257]. Low caloric intake means substantial amounts of dietary protein is utilized as energy instead of being metabolized as protein. Therefore, it seems reasonable if the increase of protein to 90 g per day had been accompanied by a nearly proportional increase in calories, the average birth weight undoubtedly would have increased even more.

Numerous other prospective studies confirm the causal relationship between poor nutrition and prematurity. One notable study by Ebbs et al. of 380 pregnant women documented the benign effect of food supplementation and nutritional education on the outcome of pregnancy [155,157]. Only those who were reasonably healthy, were in their second trimester of pregnancy, and agreed to be confined at Toronto General Hospital until delivery were included in the study, which was conducted from November 1938 to March 1941.

Thorough dietary histories for the previous seven days were taken of all 380 women upon admission into the study. All of the 170 who were found to be well nourished were provided nutrition counseling until delivery [155,157]. Two hundred and ten women were determined to be inadequately nourished. These 210 women had much higher numbers of infant morbidity and mortality in their previous pregnancies. It is also noteworthy that the family per capita income among the 210 poorly nourished women was only half that of the 170 well nourished women [157]. Ninety of the women on poor diets were selected on an alternate basis to receive food supplements from the fifth or sixth month of pregnancy up to six weeks postpartum [157]; the average duration of supplements was 4.7 months [155]. These women, 48 per cent of whom were on welfare, were of slightly lower income status than the remaining 120 women on poor diets, none of whom received supple-

ments or nutritional guidance [155,157]. The food supplementation, which consisted of 30 ounces of milk, 1 egg, 1 orange, 2 tablespoonfuls of wheat germ, and 2,000 IU of vitamin D daily (the remaining 290 women in the study received a placebo instead of the vitamin D supplement), and two pounds of canned tomatoes and a half pound of cheese weekly, increased protein intake by about 45 grams daily, calcium by 1.5 grams, iron by 15 mg, and calories by 840. The cost for supplemental food was approximately \$25.00 (1941 values) per pregnancy. There were no major differences in either age or duration of prenatal observation among the three groups.

The 170 women in the good diet group were counseled to have a daily intake of 1.5 g of calcium, 90 grams of protein, and 2,600 calories. As Table 3-10 reveals, there was little difference between the dietary intakes of the 170 women who received nutritional education and the 90 who were given supplements, whose diets were markedly improved. In the sixth or seventh month of gestation, in both the food supplementation and nutritional education groups, only 2 per cent had a daily intake of less than 60 grams of protein, and 2 per cent had less than 0.8 g of calcium daily. In contrast, among the 120 controls on poor diets, 38 per cent had a daily intake of less than 60 grams protein and 61 per cent had less than 0.8 grams of calcium.

Table 3-10
AVERAGE DAILY INTAKE OF MAJOR NUTRIENTS
BEFORE (AFTER) BEGINNING OF STUDY [155,157]

	No. of Women	Calories	Protein (g)	Calcium (g)
Poor diet whole pregnancy	120	1627 (1837)	46 (62)	0.54 (0.75)
Poor diet at start; supplement last 3-4 months	90	1690 (2424)	56 (94)	0.56 (1.61)
Good diet whole pregnancy; dietary education last 3-4 months	170	2206 (2521)	81 (92)	0.89 (1.30)

Despite the fact that the percentage of primigravidae in the good diet group (46%) was approximately 50 per cent higher than that in either the poor diet group or the food supplementation group, the rates of miscarriage, stillbirth, and prematurity (definition not specified) were similar in good diet and supplemented diet groups; in fact, the results in both were significantly lower than in the poor diet group ($p<0.02$) (see Table 3-11). The difference in prevalence of miscarriages and stillbirths between the poor diet group and both the good diet and supplemented diet groups was significant at $p=0.01$.

The data refute the generally accepted notion that primigravidas are of intrinsically high obstetrical risk [154]. They also confirm Iyenger's observations of the greatly beneficial effect of dietary supplementation even when begun as late as mid-pregnancy among poorly nourished gravidas [257].

Table 3-11
INFLUENCE OF DIET IN REDUCING RISK OF
MISCARRIAGE, STILLBIRTH, AND PREMATURE BIRTH [155,157]

<i>Type of diet</i>	<i>No. of women</i>	<i>Per cent miscarriages</i>	<i>Per cent stillbirths</i>	<i>Per cent premature</i>
Poor	120	5.83	3.33	8.33
Good	170	1.18	0.58	2.94
Supplemented	90	0.0	0.0	2.22

The only measurement which was not in accordance with the other findings was the relatively high average birth weight of infants born to women on poor diets (3,459 g) [157]. These babies weighed an average of 82.5 g more than those born to women who had been on good or supplemented diets. Such high birth weights in the poor diet group appear to be contradictory, since the women in the poor diet group were three times more likely to have a premature infant (which was probably meant by the authors to indicate the birth of an infant weighing under 2,500 g, although this is not clear) than the women in the better fed groups. Another result which seems to contradict the finding that the average birth weight was highest among the malnourished women is the fact that at the age of six months, their infants weighed, on the average, 227 g less than the infants born to the women on good diets and 269 g less than those born to mothers on supplemented diets. Inaccurate tabulation, found in other calculations in the study, may account for some of this apparent paradox in birth weight, but not all. One possible explanation of this surprisingly high average birth weight in the poorly nourished group is that miscarriages and stillbirths were more than five times more common in the poor diet group than in the other two groups. If most of these 11 pregnancies had resulted in live births, it is possible that the average birth weight of the entire group would have been lower. Also, the possibility was not excluded that a few extremely large infants due to undiagnosed or early diabetes were in the poor diet group. This is the kind of study which has to be closely examined for those features which are well enough documented for more general use in unraveling the mysteries of pregnancy nutrition. Part of the problem, of course, is the nature of sampling *per se*. The unevenness in a single database which appears incongruous when the findings in several are brought to bear is reconciled only by reference to

and detailed discussion of numerous studies in a broad scale review such as has been supplied in this and similar books. Fundamentally, there is no error or problem of sufficient magnitude within the three reports by Ebbs et al to cause dismissal from incorporation within the larger picture [155-157].

Of the first 250 babies examined at six months, there were three deaths in the poor diet group and none in the other groups [156]. Table 3-12 excludes infants with gross congenital abnormalities, rather perversely, but includes miscarriages and stillbirths in the lowest pediatric rating (*bad*), demonstrating the relation between maternal nutrition and pediatric rating at two weeks of age [156]! It is especially noteworthy that the addition of nutrition supplements during the latter half of pregnancy lessened the incidence of mortality and major infant morbidity from 14 per cent (italicized in Table 3-12) to zero.

Table 3-12

CONDITION OF INFANT AT AGE TWO WEEKS BY PRENATAL DIET [156]

<i>Prenatal diet</i>	<i>Condition</i>			
	<i>Good</i>	<i>Fair</i>	<i>Poor</i>	<i>Bad</i>
Poor	62.3%	23.7%	5.3%	8.7%
Good	72.2	23.8	1.2	3.0
Supplemented	90.5	9.5	0.0	0.0

In addition, of these 250 infants, 21 per cent of those from women in the poor diet group, compared to only 5 per cent of the infants of mothers in the other two groups, had frequent colds [155,157]. Also, the infants of mothers on poor diets were more often afflicted with pneumonia and bronchitis and had a significantly greater incidence of anemia than the other infants [155,157]. Some of these differences may be attributed to the fact that 10 per cent more women in the supplemented diet group successfully breastfed their babies [155].

The authors concluded, "The application of the principles of nutrition could not be more important in any other period of life than during pregnancy" [156].

Toverud, who established a health and nutrition station in Oslo, Norway, in 1938, also reduced the prevalence of low birth weight to 2.2 percent [536]. There were 728 women participating, from 1939 to 1943, in the program with carefully supervised pregnancies. There were other women who did not receive as much attention as the supervised patients; the low birth weight incidence for this other group was 4.6 percent, which, however, is lower than the rate of any reporting unit in the United States.

The relatively low birth weight rate at the health station was partially due to the fact that a high number of women in reasonably good health became enrolled in the program. During the same time period, the stillbirth rate at the health station was 14.2/1000; that of women who did not participate in the nutrition program but resided in the same district was 28.3/1000. In addition, from 1939 to 1944, the infant mortality rate (defined in Norway as deaths of infants under one year per 1,000 live births) for the supervised pregnancies (fourteen) was less than half that of Oslo (thirty).

There was not one case of clinical brain damage among the more than 1,500 liveborn infants delivered by mothers who attended the health station. These women also received vitamin K.

Actually, Toverud recognized the protective effects of pre-natal nutrition in the late 1920s, at which time the low birth weight incidence among illegitimate births in Norway was greater than 20 percent [575]. By improving the prenatal diets of 223 unwed mothers in 1931, Toverud reduced the incidence of underweight births to 2.0 per cent, a tenth the previous rate.

An even greater reduction – in fact, eradication – of low birth weight was achieved by Tompkins, who initiated a prospective prenatal nutritional study in 1937 which vividly demonstrated that low birth weight, stillbirth, and infant mortality largely result from nutritional deficiencies [533]. Excluding only women who had syphilis, active tuberculosis, or advanced cardiac lesions, Tompkins studied 750 pregnant women (two-thirds were clinic patients) receiving prenatal care at a single hospital. Because 82 per cent exhibited signs of nutritional deficiencies (87% had glossitis, approximately 75% had subclinical scurvy, 70% were diagnosed with polyneuritis), obstetrical management was focused primarily on nutrition.

Consequently, all of the women in the study were instructed to eat a well balanced diet, which exceeded the current Recommended Daily Allowances (RDA) for most essential nutrients, including protein, i.e., 110 g daily was recommended in contrast to the then current standard of 76 g [595]. To ensure proper nutritional intake throughout pregnancy, the consumption of five or six relatively small meals was encouraged.

Besides nutritional counseling (the majority of the clinic patients also attended special nutritional education classes), the women received vitamin supplements. It was determined to be relatively difficult to provide all of the required nutrients solely by dietary means. As the study continued, vitamin supplementation was augmented because of its demonstrated immediate effectiveness in alleviating or eliminating various complications. Admitting that: “a balanced diet for normal pregnancy has received little or no attention,” Tompkins developed and improved upon his diet and vitamin supplementation regimen as the study progressed. Recognizing the

nutritional stress of gestation (which he referred to as the "metabolic demand in pregnancy"), Tompkins stated [533],

. . . our therapeutic efforts are also directed toward improving the general nutrition of the patient, principally from natural food sources, but also with polyvitamin therapy in sufficient dosage to relieve the signs and symptoms.

A control group was represented by yearly statistical totals from the same hospital. The basic differences between the study group and the controls were the dietary instructions and polyvitamin supplements received by those participating in the prospective study. While Tompkins did not explicitly control many factors which might affect the findings in the two groups drawn from the same population, the dramatically low incidences of complications and infant deaths in the well nourished group virtually obviated the need for controls.

Not only were there no low birth weight children born to study group women, but more revealing, the smallest child weighed a most respectable 2,842 g. Extrapolating from the data provided, one can estimate that the low birth weight incidence in the control group was about 8 per cent. Had salt, an essential nutrient required for the maintenance of the increased blood volume of pregnancy, not been restricted simultaneously, and if weight gain not been controlled as well (Tompkins believed that 20 pounds represented the ideal gain), the birth weights would have undoubtedly been higher. This becomes clearer when the mean maternal weight gains are considered against the mean birth weights (Table 3-13). This shows some disjunction between maternal weight gain and birth weight which will be considered further in the discussion on The Motherwell (Scotland) Protocol (page 142). Despite the closely similar mean birth weights, however, pregnancy outcome was very different. There were no stillbirths and only three infant deaths among the study group births in contrast to 61 perinatal deaths among the controls (Table 3-14).

Tompkins also linked inadequate nutrition, particularly vitamin A deficiency, to spontaneous abortion.

The protective effects of maternal nutrition in preventing infant mortality

Table 3-13

EFFECT OF CALORIC INTAKE AD LIBITUM BEYOND HIGH PROTEIN
INTAKE AND MULTIVITAMIN SUPPLEMENTATION ON MEAN
MATERNAL WEIGHT GAIN AND MEAN BIRTH WEIGHT [533]

	<i>Maternal weight gain</i>	<i>Birth weight</i>
Weight gain limited to 20 pounds (8.9 kg)	21.8 lbs	3311 g
High protein diet but calories ad libitum	31.2 lbs	3221 g

Table 3-14
EFFECT OF NUTRITION ON LOW BIRTH WEIGHT,
STILLBIRTH, AND INFANT MORTALITY [533]

Category	Study group		Control group		Significance of Difference
	Number	Rate per 1000	Number	Rate per 1000	
Births under 2268 grams*	0	0.00	37	49.3	$p < 10^{-8}$
Stillbirths	0	0.00	20	26.7	$p < 10^{-6}$
Infant deaths	3	4.00	41	54.6	$p < 10^{-7}$

*5 pounds. There were 750 pregnancies in each group.

and proneness to morbidity, as documented by Ebbs [155-157], Tompkins [533], Toverud [536], and others had been observed even earlier by Mellanby [364]. "Nutrition," Mellanby declared, "is the most important of all environmental factors in childbearing whether the problem is considered from the point of view of the mother or that of the offspring."

A 1944 well-controlled prospective study in Glasgow of 1,000 women, all pregnant during approximately the same period, provided further evidence of the relationship between malnutrition and low birth weight and infant mortality [85]. Five hundred women attending the same prenatal clinic received dietary counseling during the last three months of pregnancy. A control group of 500 women was acquired by selecting the name of the clinic charts following that of each of the 500 women in the study group. As expected, there was little difference in either age or parity between the groups.

Cameron and Graham showed that just three months of nutrition counseling without food supplements promotes a significant decrease in low birth weight ($p < 0.05$) and an effective decrease in mortality ($p < 0.05$) [85] (Table 3-15).

They concluded:

Neonatal mortality has shown very little improvement. By far the largest factor in these neonatal deaths is prematurity and of these premature deaths, roughly 50% occur in the first 48 hours. Most of these deaths are among the smallest and most weakly infants and it is unlikely that medical science even at the cost of more research and the spending of much time and money will save more than a few of them. A more rational method of approach to the problem would seem to be that of prevention. [85]

A more recent prospective nutrition supplementation study showed that the low birth weight incidence was significantly lower (at approximately the 3% level of significance) among women who received supplements [535]. Although the participants were not initially selected at random, women were placed in the control or one of three supplement groups on a random basis after controlling for race, age, and parity.

Table 3-15
EFFECT OF NUTRITIONAL STATUS ON
BIRTH WEIGHT AND INFANT MORTALITY [85]

Group	Pregnancies				Per cent	Total perinatal mortality
		Low birth weight	Stillbirth	Infant mortality		
Study	500	6.2	4.2	1.6	5.8	
Control	500	10.0	7.2	2.0	9.2	

Of a control group of 198 women who received no supplements, the low birth weight incidence was 11.1 per cent against 6.4 per cent for the 641 women who received vitamin and/or protein supplements. Some of the 641 women received additional vitamins which provided approximately three times the RDA for nonpregnant women, and others received a supplement consisting of 50 g of high quality protein and 1.5 g of calcium. The remainder of the 641 women received both supplements. The programs were begun at the first prenatal visit and were continued to delivery.

The difference between birth weights of infants born to women receiving supplements and those of the controls would likely have been much more significant had a larger number of women receiving the extra protein taken all of their allotted supplements. The authors declared:

Examination of the individual records of the patients taking protein supplement only shows that the poor weight status of babies of a few patients, who took less than half of the intended amount of the protein supplement, was responsible for the low average weight for the entire group. [535]

An association was found between nutrition supplementation and birth weight and length of gestation. Of the infants born to women who did not receive protein supplements, 9.16 per cent weighed less than 2,722 g at birth. In comparison, only 3.23 per cent of the infants delivered by women who were provided protein supplements weighed under 2,722 g at birth. Women who received protein and vitamins delivered significantly later than women in the other three groups ($p < 0.05$). Less than 4 per cent of the supplemented women delivered more than one week before term.

In addition, prepregnancy weight and birth weight were highly correlated, signifying that underweight women may have nutritional deficiencies. Normal weight or obese women, who have more caloric reserves than underweight women, are less likely to utilize protein as energy than women who are underweight. Table 3-16 reveals, especially among women underweight at their first prenatal visit, that protein and/or vitamin supplements markedly

Table 3-16
UNDERWEIGHT BIRTHS ACCORDING TO PRE-PREGNANCY WEIGHT [535]

<i>Prepregnancy weight status</i>	<i>Supplemented group</i>	<i>Control group</i>	<i>Whole study</i>
0-5 per cent underweight	5.0% (363)	6.3% (126)	5.3% (489)
>5 per cent underweight	8.9% (190)	22.2% (54)	11.9% (244)
Totals	6.3% (553)	11.1% (180)	7.5% (733)

decrease the risk of low birth weight. The data, given as percentages of low birth weight, are significant at the 1 percent level ($p=0.01$). In parentheses are the number of pregnant women in each group. Women at least 15 percent above their standard (median) prepregnancy weight at registration had a period of gestation significantly greater than women within 5 percent of their standard weight ($p<0.001$). Infants delivering within one week of term, from women of the former weight group, were 209 g heavier at birth than from mothers of the latter group.

An association was also found between hemoglobin level at the initial prenatal visit (a marker for iron sufficiency and indirectly for protein intake) and birth weight. Low birth weight accounted for 13.2 per cent of births in 91 women with the lowest initial hemoglobin level; the frequency in the 202 patients with the highest initial hemoglobin level was 5.4 per cent. The difference, which is statistically significant, would probably be less striking if the hemoglobin levels had been controlled for socioeconomic status [535].

Grieve found a remarkable reduction in pregnancy complications and perinatal mortality when the hemoglobin level was maintained at 12 g/dl or better [211].

The limitation of an adequate hemoglobin level as an indicator of good protein nutrition is shown by the dramatic case report of Gormican and Shrout [206]. A 21-year-old woman with adenocarcinoma was treated by radical pancreateoduodenogastrectomy with continuity reestablished by end to side pancreaticojejunostomy, posterior gastrojejunostomy, and cholecystostomy. Intensive dietary therapy was instituted. Four months later, she became pregnant. Her daily protein intake was 40 g, half of which was of vegetable origin. Pregnancy weight gain was about 7.7 kg. Hemoglobin was maintained as 12 g/dl only by a course of iron dextran injections. She gave birth to twins in the 36th week. By twin standards [81], the infants were of good size and length (first twin, 2,285 g and 48.9 cm crown to heel length; second twin, 1,956 g and 45.7 cm) with Apgar scores of 9 and 10, respectively. Nevertheless, in the second year of infancy, it became clear that both were profoundly retarded. Gormican and Shrout applied singleton birth

standards erroneously to obtain their published percentile ratings. By contrast, Grieve's avoidance of iron dextran to maintain hemoglobin levels is commendable; otherwise, protein deficiency can be masked.

Hunt's study documented the immediate effects of even a limited nutritional education program in improving the nutritional status of gravid women [251]. The study involved Spanish speaking women who attended one or two county prenatal clinics from 1972 to 1974. Only women who registered for their initial visit no later than the 21st week of pregnancy and did not have diabetes or heart disease could participate in the study. The 344 women in the study represented approximately 80 percent of the clinic population. The average monthly income was less than \$360, 1975 value.

Using a random selection process, Hunt et al. assigned half to a control group and half to a nutrition education group [251]. The second group went to an average of three nutritional education classes during their pregnancies. The two groups of women showed remarkably little difference in age, income, family size, educational advancement, height, weight before pregnancy, and weight gain during gestation. Forty controls and 25 in the study group were excluded. The excluded cases were 24 who delivered "early," 16 who delivered after completion of the study, 22 who moved or could not be contacted, and three women whose pregnancies were terminated or suffered miscarriage. No other data were given on the characteristics of the excluded cases.

For all 279 women (147 in the treatment group, 132 controls), 24-hour dietary recalls and biochemical tests were taken at the initial visit (average, the 18th week of gestation) and the final one (average, the 35th week). The dietary evaluations, based strictly upon food intake rather than food plus supplements, revealed that 88 per cent of the women initially were getting less than two-thirds of the RDA of at least one of the measured nutrients. The greatest such deficiencies were iron (77% of the women received less than two-thirds the RDA of iron; the authors claimed this RDA is probably excessive), vitamin A, thiamine, calcium, and calories.

Initially, 32 per cent of the control women and 26 per cent of the treatment group had been taking extra vitamins and/or minerals. The routine prescription of vitamin and mineral supplements to all women led to a final (last prenatal visit) level of supplementation of 79 per cent in each group, a significant increase ($p<0.005$). Biochemical tests showed that vitamin and mineral supplements have a profound effect in improving nutritional status. Among those who took supplements, only 3 per cent were deficient in three or more nutrients, whereas half of those admitting they failed to take supplements exhibited multiple deficiencies. Plasma carotene and serum folic acid increased significantly ($p<0.01$) by the final prenatal appointment

for both groups. A seeming paradox was found in the hematocrit which increased more among the controls ($p<0.005$) than for those receiving nutritional education ($p<0.05$); this may be due to a more marked increase in blood volume in the treatment group.

Perhaps the most dramatic finding was the substantial decrease in nutritional deficiencies (defined as an intake of less than two-thirds of the RDA for various nutrients and measured by 24-hour dietary recall) among the 147 study group women. While 47 per cent of these individuals exhibited deficiencies in at least three nutrients at their initial appointment, only 33 per cent had similar multiple deficiencies at their last visit ($p<0.02$). In contrast, 52 per cent of the control group showed such deficiencies initially, and 50 per cent still did so on the last dietary assessment. Equally revealing, the women in the study group exhibited significant increases in more nutrients than those in the control group (Table 3-17). In addition, they scored much higher ($p<0.005$) in an examination on nutritional knowledge.

Table 3-17
RELATIVE IMPROVEMENT IN DIETARY INTAKE THROUGH
NUTRITIONAL EDUCATION OF PREGNANT WOMEN [251]

<i>Factor</i>	<i>Study group</i>	<i>Control group</i>
Thiamine	0.05	NS
Calories	0.05	0.02
Vitamin C	0.02	NS
Niacin	0.02	NS
Carbohydrates	0.01	0.02
Calcium	0.01	0.01
Protein	0.01	NS

Values are p or significance level; all other nutrients tested were without significance in either group

The authors concluded, "Emphasis should be placed on including short nutrition education programs in public health nutrition" [251]. As confirmed by the improvements in maternal and infant health, documented in numerous studies discussed throughout this book, comprehensive nutrition education programs would undoubtedly yield an even greater improvement in nutritional status.

A recent double blind supplementation study in Guatemala has shown that food supplementation during pregnancy substantially increases birth weight and decreases infant mortality [219]. The participants lived in conditions of abject poverty, the median annual family income being approximately \$200 in 1970 value [219]. The typical prenatal diet before the study was 1,500 calories and 40 g of protein; average weight gain was about 6.7 kg [309-313]. Few homes had sanitation [219]. Pregnant women in two

villages were free to go to a special center to drink a supplement consisting of 91 calories, 6.4 g of protein, and vitamins and minerals per 100 ml [46,219,311]. Women in two other villages, with approximately the same previous caloric intake and health status and about the same height as the women in the first two villages, were given a supplement which consisted of 33 calories, vitamins, and two minerals per 100 ml [219]. Throughout pregnancy, the amount of the supplement, the type unknown to all participants, was measured and recorded.

The analysis of birth weight involved 288 of the total of 433 births [219]. Multiple births, those for which the duration of gestation was not estimable, and premature births made up the 145 births excluded from the analysis. Had the premature births been included, the finding that birth weight is substantially increased by food supplements undoubtedly would have been even stronger. Birth weight, even after adjustment for maternal height, maternal weight in the first trimester, age, parity, and sex of the infant (the investigators believed that such variables are unrelated to nutrition), increased as the maternal caloric intake went up [219]. Also investigated were other factors which might have caused an increase in birth weight or influenced the effect of caloric supplements on birth weight. Neither socio-economic status nor degree of cooperation accounted for the increase in birth weight. Even prepregnancy weight, which, as expected, was highly correlated with birth weight ($p < 0.01$), accounted for only some of the association between supplementation and birth weight [219].

The dramatic effect of caloric supplementation on increasing birth weight is shown in Table 3-18 [219]. There were 69 women who received more than 31,000 supplementary calories; not one gave birth to an underweight child. Moreover, 19 per cent of these infants were over 3.5 kg at birth. Note that the incidence of low birth weight among women ingesting less than 5,000 supplementary calories was nearly four times as high as among those with at least 20,000 additional calories (the two right hand columns in Table 3-18, when combined, show 4 low birth weight infants from 117 pregnancies, or 3.42 per cent). The paradox of a nonlinear result in relation to calories is

Table 3-18
EFFECT OF CALORIC SUPPLEMENTATION ON LOW BIRTH WEIGHT [219]

	<i>Caloric supplementation</i>			
	<5,000	5-19,999	20-31,000	>31,000
Pregnancies	82	89	48	69
Low birth weight	11 (13.4%)	6 (6.74%)	4 (8.33%)	0 (0.0%)

The two right hand columns were combined in the first edition, as Table 3-XIV.

likely a consequence of small samples and arbitrary choices for the range of supplemented groups.

A more recent analysis of this study revealed there were no stillbirths among the 199 who received the highest caloric supplementation [219,309-313]. Stillbirth accounted for 6.6/1000 live births among the 454 women who took the least supplementation. The risk of mortality during each of the four quarters of the first year of life was markedly lower among the 199 women who received the most supplementary calories. It was found that *infant* mortality was four times greater among the low birth weight infants than among those weighing over 2,500 g at birth [219]. The higher rate of infant mortality among low birth weight infants was not altered by the level of supplementation. The reduction in infant mortality by supplements was primarily due to the reduction in the frequency of low birth weight (Table 3-19).

Table 3-19
PERINATAL AND INFANT MORTALITY BY
DEGREE OF CALORIC SUPPLEMENTATION [219]

Supplement	Women	Stillbirths	Post natal mortality		
			0-6 months	6-9 months	9-12 months
High	199	0 (0.0%)	6 (3.0%)	2 (1.0%)	0 (0.0%)
Low	454	3 (0.66%)	24 (5.3%)	5 (1.1%)	3 (0.7%)

The total mortality for the high supplementation was 7/199 or 3.52 per cent, whereas total mortality for low supplementation was 32/454, or 7.05 per cent, the latter exactly twice the former.

The average birth weight from women taking the protein/calorie supplement was 104 g more than of women taking the supplement which had no added protein [219]. This difference in birth weight, which was not statistically significant, would probably have been greater if the protein, which consisted of a corn-based cereal, had been of higher quality with respect to essential amino acids. The greatest difference in birth weight occurred among women ingesting at least 20,000 supplementary calories during pregnancy. The best supplemented women, those receiving both calories and protein (73 cases), had an average birth weight 142 g greater than 44 women who took just the calorie supplement. A different study would be designed now, but the data indicate strongly the caloric intake was the main limiting nutritional factor affecting birth weight. Since these women were apparently calorie deficient, some of the extra protein (a total of 1,406 g for those taking 20,000 supplementary calories) was used for energy rather than tissue synthesis. This point was emphasized by Iyenger [257]. Of the nine women

who did not participate in the study during a previous pregnancy but who ingested more than 20,000 supplementary calories in a subsequent pregnancy, the increase in birth weight in the subsequent pregnancy was 400 g, a difference highly significant at the 1 percent level. In contrast, among the eight women who did not take any of supplements during a successive pregnancy, the most recent child weighed, on the average, 50 g less than the first, a trivial difference.

The authors considered the hypothesis that the increased birth weight caused an increase in appetite for the supplements, a theory seriously promulgated by Darby et al. [118,119,360-362]. Although males outweighed females by 73 g at birth, there was no major difference in the percentage of male births according to degree of supplementation. The authors stated: "The argument that greater intrauterine growth is the cause and not the result of increased supplement ingestion is thus not substantiated [219]." In addition, no relationship was found between time of supplementation and birth weight. Differences in birth weight between the well supplemented and poorly supplemented pregnancies were similar, regardless of the trimester(s) of greatest supplementation. The authors concluded: "Our data suggest that the optimum time to begin supplementation is as early as possible in pregnancy and that supplementation should continue throughout pregnancy" [219].

Another study of 671 single births in the same four Guatemalan villages considered the effects of food supplements during pregnancy, lactation, and the first fifteen months of childhood on infant mortality and the growth and development of the children [309-312]. Many children received the same type of protein/calorie supplement from six to fifteen months of age given to the mothers.

Physical growth retardation, which was assessed at age fifteen months, was defined as weight under the tenth percentile of the population distribution (7.2 kg for males and 6.5 kg for females). Fifteen-month-old children scoring below the tenth percentile on a composite scale of psychological exams were classified as low psychological test performance. Children who received the benefit of the protein/calorie supplement, either prenatally or postnatally, had a much lower risk of substandard size or to be psychologically handicapped than those who received the caloric supplementation. The children with physical growth retardation were significantly more likely to have low psychological test performance ($p<0.01$).

The frequency of physical growth retardation was more than twice as high among the 373 children born to mothers who received the smallest amount of caloric supplementation (12.3%) compared to the children from the 84 mothers receiving the most supplementary calories (6.0%). In addition, low

psychological test performance was four and a half times as high in the former group (11.0%) as in the latter (2.4%). These differences could not be accounted for any socioeconomic factors, maternal characteristics, or childhood morbidity.

The authors declared:

Intervention programs (in poor rural populations) designed to reduce infant mortality have generally focused on the control of infectious diseases through adequate health services and paid little attention to nutrition. These results demonstrate that nutritional interventions can help to reduce infant mortality. [219]

Preliminary data from a similar prospective study confirm the causal relationship between nutritional supplementation and birth weight [114]. Results after five years of a double blind protein supplementation study in Taiwan showed a significant difference in birth weight for infants from pregnancies supplemented by protein and vitamins compared to infants after pregnancy supplements which provided only calories and vitamins.

Both groups of women took the assigned supplement in the presence of a nurse who did not know which supplement it was. The average birth weight of infants of women who received the protein supplement was 150 g greater than older siblings born before the mother participated in the food program [114].

A food supplementation program in a low income Mexican agricultural village where nearly all families were chronically malnourished also resulted in substantial improvements in size and development of the offspring [322]. The children of women whose diets were supplemented during pregnancy were 8 per cent heavier at birth than village children born earlier. During infancy, these children exhibited superior language development compared to other children of the same age. At age one year, the children of the well fed women were said to be three times more active than their peers; at age two years, they were four times more active.

RETROSPECTIVE STUDIES

Even in the absence of food supplementation, sound nutritional education can result in a marked reduction in the frequency of low birth weight. Among primigravidas delivering at a county hospital from July 1963 through December 1967, low birth weight among women participating in Brewer's nutritional education program was nearly a fifth that seen in women of similar economic status on weight control and salt restriction regimens [61] (Table 3-20). The data show that the probability that the nutritional education program did not result in a decrease in the low birth weight rate is less than one in a billion.

Table 3-20
INFLUENCE OF NUTRITIONAL EDUCATION ON
LOW BIRTH WEIGHT IN FIRST PREGNANCIES [61]

<i>Participants in nutrition classes</i>	<i>Number of infants</i>	<i>Low birth weight (percent)</i>
Yes	321	9 (2.8)
No	1237	169 (13.7)

None of the 318 primigravidae in the nutritional education group had premature placental separation, a factor for neurological impairment in the newborn. There were three sets of twins. The low birth weight frequency among all women who participated in the program, primigravidae and multigravidae, was 2.2 per cent.

In reviewing this dramatic decline in the low birth weight rate which resulted from sound nutritional education, Charles U. Lowe, then scientific director of the National Institute of Child Health and Human Development, declared:

These conclusions challenge the conventional wisdom, which demands constraint on weight gain by caloric restriction, a limitation of salt intake, and use of saline diuretics. None of these were used in the Brewer series . . . Why is our prematurity rate rising, a factor of life in no other advanced nation? The answer may well lie in our prenatal regimens. It looks as if we can make real progress on both questions merely by feeding pregnant women. [340]

Retrospective studies do not have the same analytic power as prospective protocols [294], but some retrospective nutritional studies provide meaningful documentation of the relationship between malnutrition and reproductive casualty.

Prior to their prospective study, and during World War II, Cameron and Graham undertook a retrospective analysis of the diets of mothers of 300 infants. This study validated the conclusions of others who had shown poorly nourished women tend to have low birth weight and stillborn infants [85]. After delivery, in hospital, mothers of 100 stillbirths, 100 low birth weight infants, and 100 normal infants were asked about their diet during the last three months of pregnancy. To control for other factors, Cameron and Graham selected 300 other women at random from the same hospital. In addition, dietary histories of the last trimester of pregnancy revealed accurate information as a result of wartime rationing.

As shown in Table 3-21, there was little difference in nutrition of women who delivered stillborns and those who gave birth to low birth weight infants, although the diets of the mothers of low birth weight babies were

Table 3-21
INFLUENCE OF NUTRITION ON PERINATAL
SURVIVAL AND BIRTH WEIGHT [85]

Factor	Optimum intake (per authors)	Approximate daily intake by group		
		Stillbirth	Low birth weight	Term size
Calories	2,500	1,644	1,710	1,946
Carbohydrate (g)	350	207	217	217
Fat (g)	80	61.4	64.9	80.4
Protein (g)	90	52.4	54.5	72.1
High quality protein	50	27.4	29.9	45.9
Calcium (g)	1.5	0.7	0.8	1.2
Phosphorus (g)	2.0	0.9	0.9	1.4
Iron (g)	15.0	9.0	9.0	11.0

somewhat superior. The carbohydrate intake in all three groups was nearly identical. Mothers of full-term, normal infants had been on diets much higher in calories, fat, protein (especially high quality protein), calcium, phosphorus, and iron than mothers of stillborn or underweight infants.

Thorough analysis of the diets of 404 low income women in the 1950s showed significant correlations between poor dietary intake and reproductive casualty [266]. Many of the women, whose diets consisted largely of white bread and potatoes, were deficient in many nutrients, notably calcium and protein. They attributed the poor diets to lack of nutritional knowledge rather than low income.

The authors, finding that protein consumption seemed to be the most accurate indicator of the quality and quantity of the general diet, divided the 404 women into five groups per estimated daily protein intake. Thirty-seven women, the best fed gravidas, had a daily protein intake of more than 85 g; 87 women, the next best nourished group, had protein intake of between 70 and 84 g; and 103 women had 60 to 69 g. The two worst groups had intakes of 50 to 59 g (101 women) and under 50 g (76 women) of protein, respectively. From the highest to the lowest protein intake group, there was a corresponding decline in calories, vitamins A, B₁, B₂, and C (the only vitamins estimated in the diet), iron, and, especially, calcium (Table 3-22).

Striking relationships between diet quality and birth weight, mortality, and congenital defects were evident. Low birth weight occurred in 13.16 per cent of the 76 women on the worst diet. Low birth weight accounted for 9.6 per cent of the 177 women receiving less than 60 g of protein daily, significantly higher than for the 227 women (3.96%) ingesting at least 60 g daily ($p < 0.01$). A set of twins in the best fed group were both underweight, despite a combined weight of 4,759 grams.

Table 3-22
PERINATAL CONSEQUENCES OF SCALED PROTEIN
DAILY INTAKE DURING PREGNANCY [266]

<i>Protein intake</i>	<i>Number of women</i>	<i>Low Birth Weight (per cent)</i>	<i>Stillbirth</i>	<i>Low Birth Weight: Neonatal mortality</i>
>85 grams	37			
70-74	87	9/227 (3.96)	0	0
60-69	103			
50-59	101	5 (4.95)	0	2
<50	76	12 (15.79)	1	5.
<60	177	17 (9.60)	1	7

Of the nine low birth weight infants of mothers who consumed at least 60 g of protein a day, there were no stillbirths, neonatal deaths, or congenital anomalies. In contrast, among the seventeen low birth weight infants of the women ingesting less than 60 g of protein daily, there were one stillbirth, five neonatal deaths, and four infants with severe congenital defects.

Even slight maternal dietary deficiencies can result in subtle but permanent physiological impairment in the offspring [49,117,252,324,589,619]. A pregnant woman whose diet is markedly deficient in one or more of the lipotropes, such as vitamin B₁₂, folic acid, choline, or methionine, may give birth to a child with an abnormally small thymus gland [589]. Retarded growth of the thymus gland is often accompanied by malfunction of thymus dependent lymphocytes, increasing the chance of infections.

THE VANDERBILT COOPERATIVE STUDY

There are some studies which do not agree with those noted so far. However, retrospective analysis of one study, which purportedly demonstrated that maternal nutrition plays little or no role in the outcome of pregnancy, shows how many such studies are found to have faulty design, distorted data analysis, or both.

Very typical of these studies is the Vanderbilt Cooperative Study of Maternal and Infant Nutrition [118,119,360-362]. Self selection was the main bias of the study, precluding valid comparisons. Although Darby et al. and McGanity et al. claimed that "the sample was unselected," the large majority of the 2,046 pregnant women, all white, had reasonable financial means.

Moreover, most of them were well nourished prior to pregnancy and,

excepting cases in which severe dietary restrictions had been imposed upon them by medical staff, were on adequate or marginally adequate diets during gestation. The women in the study, conducted from September 1945 to February 1949, had an average daily intake of 72 g of protein, 1.1 g of calcium, and 13.5 mg of iron. Few, if any, participants had dietary deficiencies of the degree described by Ferguson, who studied dietary intakes of low income pregnant women from 1947 to 1948 [173].

The 2,046 women were comparatively well nourished as was shown by relatively infrequent toxemia (4.5% preeclampsia, 0.5% eclampsia) and low birth weight (6.7%), less than the 1950 national rates of 6.5 per cent for preeclampsia, 0.7 per cent for eclampsia, and 7.2 per cent for low birth weight in whites. (The prevalence was 10.2% for nonwhites). McGanity et al., inferring that the women in the study represented all socioeconomic classes, falsely concluded: "An adequate diet is readily attainable from food sources in all sections of the country without the need of supplementation" [362].

Subsequent studies and nutrition surveys have documented the extent of poverty and malnutrition afflicting large numbers of Americans, including those in the Nashville area, the site of the Vanderbilt study [586,588].

The authors' conclusions, many of them tenuous and inverted, are not supported by their data. Many complications of pregnancy, which will later be shown to be caused by poor nutrition, were more prevalent among the women consuming deficient diets. There were 24 women with premature separation of the placenta. Their first trimester dietary intake, on average, consisted of 420 calories, 13.3 g of protein, and 3.1 mg of iron less than the women who did not have *abruptio placentae*. In addition, low birth weight was twice as frequent among poorly nourished women. While the authors argued in Ptolemaic fashion that obstetrical complications caused the dietary intake to be inadequate, their data actually are in accord with those of previous studies which demonstrate a definite relationship between maternal nutrition, the course of pregnancy, and birth weight.

The 103 women with toxemia (93 preeclampsia, 10 eclampsia) had a significantly lower intake of protein, iron, and niacin in all trimesters ($p=0.05$). Because women who were preeclamptic "gaining weight rapidly," or obese were placed on low calorie diets, they ended up with a significantly lower caloric intake during the last trimester. Although it is apparent that the deficient diets caused the toxemia, the authors concluded that "... the lower nutrient intake of the toxemic women appears to be a result rather than a cause of the condition (toxemia)" [360].

The fact that 35.3 per cent of the preeclamptics were placed on 900 calorie diets at some time during late pregnancy because they were "obese" demonstrates that many of the cases of toxemia were iatrogenic.

Nevertheless, the authors erroneously concluded caloric requirements during pregnancy, as "commonly understood," are excessive and that toxemia is caused by obesity.

Chapter 4

THE MOTHERWELL PROTOCOL

THE INVESTIGATIVE PROTOCOL of James Francis Kerr Grieve, B.S., M.B., Ch.B. (1912-1991), designed to determine the effect of dietary control on obstetric outcome, yielded an extraordinary amount of data. The mass of information rivals the historic effort of Ignaz Philipp Semmelweis, M.D. (1818-1865) on puerperal sepsis, when reduced to the format of a single volume book [482]. Grieve collected data for 38 years, almost three times the active investigative career of Semmelweis. He was able to publish several brief papers [211-213] but not the bulk of the work. This chapter is taken from a 1,200 page typescript version with several hundred, often detail-laden, tables. A greatly shortened summary of Grieve's unpublished manuscript is the best to be hoped for in the context of this book.

He was known to his family, friends, patients, and colleagues as Doctor Kerr Grieve. He was born in Rutherglen, Scotland, near Glasgow, and received a Bachelor of Science (Anatomy and Physiology) in 1932 and a Bachelor of Medicine and Surgery in 1935 from the University of Glasgow. He received training in ophthalmology, pediatrics, and gynecology and midwifery prior to becoming Resident Obstetrician at Motherwell Maternity Hospital, August 1, 1938. His early obstetrical career was interrupted by military duty in Egypt during World War II, 1941-1946, but patient information from those years was available and analyzed by him. He was uncommonly active in civic affairs and became the regular organist for Kenmore Kirk near Aberfeldy for many years in the autumn of his life. His early personal career touched most of the remembered names of midcentury Scottish obstetrics. Midwifery was taught and discussed vibrantly in Scotland in his formative years, with remarkable tolerance for what might pass on retrospection as either eccentricity or eclecticism. One might doubt whether his protocol would gain approval under

current rules of American Institutional Review Boards. It is important to present his observations and commentaries for this reason alone as many are of interest. Some probe deeply into the assumptions, both current and past, which many seem to take for granted or consider as established fact.

His attention to detail combined with excellent record keeping exceeded the common experience and embraced gynecologic aspects of his practice as well. Three general categories will be considered here: (1) a summary of obstetrical results, (2) comparisons of his data to Scottish health records with commentary by several of his immediate contemporaries, and (3) analysis in the context of the pathophysiology of pregnancy. The Motherwell Protocol has to be examined in the light of biological plausibility, as will be done for the WIC program in the United States (Chapter 6).

Kerr Grieve undertook a series of exploratory studies prior to formulating the operational protocol. These studies tested other ideas on the management of labor as well and led to his abandonment of vaginal and rectal examinations for labor progress. He and his staff came to rely on bedside evaluation with occasional *soft touch* assessment of the tone of uterine contractions. As will be described, the only vaginal examination used was when the placental membranes were ruptured. His preliminary work also led to abandoning x-ray pelvimetry.

THE ASSESSMENT METHOD

He incorporated the data kept at Motherwell 1940-1947 as historical controls. The principal effort during the interval 1948-1959 was to establish the details of what he termed the *obstetric equation*, the *gestational index*, and the *diet index*. These were the measurement criteria for assessing dietary success or failure. The final several years of this middle period, however, differed little from the seventeen years of the fully developed protocol.

The term *obstetric equation* refers to a narrative description of factors applicable to the outcome of pregnancy. It incorporates these features: gestational failure, parturient failure, lactational failure, gestosis (the European term for preeclampsia/eclampsia), abruptio placentae, inexplicable fetal death, avoidable fetal death, lethal cord prolapse, lethal prematurity, and fetal distress. No attempt was made to quantify these concepts and findings, some of which would be defined differently or better understood pathophysiologically today. The factors were placed into a conceptual equation:

$$\text{Morale} + \text{Physique} + \text{Passages} + \text{Passenger(s)} + \text{Powers} = \text{Mother} + \text{Baby}$$

While these features all have certain core meanings, some of which qualify

as common sense attributes, Kerr Grieve made the special point that *physique* was meant to include both systemic maternal prenatal and gestational aspects of health and adaptation.

The term *gestational index* was devised to account for certain specifics of food intake as related to hemoglobin levels. Kerr Grieve used hemoglobin as a marker for protein intake. His preliminary work led him to conclude that iron supplementation alone would not increase the hemoglobin level during pregnancy.

The gestational index contains three elements: (a) hemoglobin level as an index of protein intake, (b) average weight gain per week as an index of water retention, and, therefore, of starch intake, and (c) the actual weight of the mother before delivery related to an expected final weight. The core elements in the gestational index are presented in Table 4-1.

Table 4-1
THE GRADING SCHEME FOR THE GESTATIONAL INDEX

Hemoglobin (Coded as B)	
$\geq 12.0 \text{ g/dl}$	= grade 1
$10.0-11.9 \text{ g/dl}$	= 2
$\leq 9.9 \text{ g/dl}$	= 3
Weight gain per week (Coded as W)	
$\leq 250 \text{ g/week}$	= grade 1
$251-500 \text{ g/week}$	= 2
$\geq 501 \text{ g/week}$	= 3
Final weight vs. expected final weight (Coded as FW)	
Actual weight \leq expected weight + 3 kg	= grade 1
Actual weight = expected weight	= 2
Actual weight \geq expected weight + 6 kg	= 3

These are related through this representational equation:

$$\text{Hemoglobin} + \frac{\text{Weight gain (kg)}}{\text{Weeks}} + \frac{\text{Final weight (kg)}}{\text{Expected final weight (kg)}} = \text{Index}$$

The protein-blood factor was further modified when iron supplements or blood transfusions were employed. This was a necessary adjustment using the hemoglobin level as a surrogate for protein intake. Treatment prior to mid-gestation (20 weeks) was discounted. Treatment after 20 weeks prompted an adjustment in the observed hemoglobin level as follows: (1) each iron treatment for 1-4 weeks, and (2) each transfused unit of whole blood or packed erythrocytes (RBC) were ranked as 1.0 gram/dl to be subtracted from the actual hemoglobin level. Thus, a hemoglobin of 10.2 attained by two units of packed cells would be corrected to an index value of 8.2. Transfusions were actually used but rarely and iron supplements were closely managed so that

the index would be an appropriate marker for protein intake.

The final weight (FW) grade was blended into the weight gain (W) as follows; the final coded weight grades are italicized in the matrix boxes of Table 4-2.

Table 4-2
SUMMARY OF WEIGHT CODES

Final weight (grade)	Weight gain per week (grade)	
	1	2
1	W1	W2
2	W2	W3

All other combinations were regraded as W3. Data were sufficient for 15,755 out of 15,820 maternities (99.59 per cent).

Kerr Grieve agreed that it was simplistic to use hemoglobin as a proxy for protein but countered by noting a relative ease and fair reproducibility of the data. He found it related to blood volume and diastolic blood pressure, and, rather remarkably, to be inversely related to premature onset of labor. If acute preeclampsia and eclampsia were present, and the diastolic blood pressure was in the range of 100-110 Torr, sometimes higher, the hemoglobin was invariably around 12.0 gm/dl. This he considered to be a maladaptive adjustment which was confirmed usually during the puerperium; the hemoglobin would fall rather quickly to 10.0 gm/dl or less, despite any puerperal diuresis. Such a finding justified reducing the hemoglobin element in the index by one grade point.

There were two other observations which Kerr Grieve took into consideration: (1) failure to gain weight on a conventional well balanced diet is a sign of potential fetal disturbance, and (2) an undue increase in weight indicates that food and fluid intake were pathophysiologic, with other consequences.

Kerr Grieve modified the code letters and numbers in his summary text, but not in his tables. Because the modified scheme is simpler and more direct, it has been adopted here (Table 4-3).

While this may seem unduly complex, it has an element critical for outcome measurement: *systematized stratification*. In fact, the scheme can be made quite simple in this way:

1. If both hemoglobin and weight gain are graded as 1 or one is a 1 and the other a 2, then the pregnancy success category is *high*.

Table 4-3
PREGNANCY DIET SUCCESS CATEGORY CORRELATED
WITH HEMOGLOBIN AND WEIGHT GAIN FACTORS

<i>Modified hemoglobin factor</i>	<i>Modified weight gain factor</i>	<i>Gestational index</i>	<i>Pregnancy success category</i>
B1	W1	1	High
B1	W2	2a	High
B2	W1	2a	High
B2	W2	2B	Medium
B1	W3	3	Low
B2	W3	3	Low
B3	W1	3	Low
B3	W2	3	Low
B3	W3	4	Poor or very low

2. If both hemoglobin and weight gain are graded as 2, then the pregnancy success category is *medium*.
3. If either factor is graded as 3 and the other is a 1 or 2, then the pregnancy success category is *low*.
4. If both hemoglobin and weight gain are graded as 3 then the pregnancy success category is *poor* or *very low*.

MANAGEMENT OF LABOR AND DELIVERY

Kerr Grieve described planned surgical induction of labor as the final act of preventive obstetrics. It might seem to be paradoxical to promote maximal use of surgical induction to start the first stage of labor whilst eschewing other mechanical interventions: (1) vaginal and rectal examination for assessment of the progress of labor, and (2) Crede's maneuver for placental delivery in the third stage. The obstetrical objective was to keep the size of the fetus below certain limits to facilitate vaginal delivery, thus keeping use of abdominal section to an absolute minimum. Ten thousand six hundred and sixty five surgical inductions were performed over the course of the Motherwell Protocol after 1960 with only 36 sections for failed surgical induction, or 0.3376 per cent (Table 4-4) (Figure 4-1).

Surgical induction of labor was performed under strict rules of technique.

Table 4-4
SECTION DELIVERIES FOR FAILED LABOR INDUCTION

<i>Inductions</i>	<i>Sections for failed induction</i>	<i>Per cent</i>
10,665	36	0.3376

First, the operation was performed only in the delivery room or operating theater. *Second*, rapid abdominal examination is done with the patient in dorsal decubitus; she is then turned to the lateral decubitus while the operator scrubs and is gloved. This is to minimize postural pressure on the inferior vena cava to the minimal time. *Third*, the woman is returned to a dorsal decubitus with the buttocks elevated to facilitate vaginal entry of the Drew-Smythe catheter. The perineum and vulva are prepared with topical antiseptic. *Fourth*, bimanual examination determines size of fetus, presentation, the physical characteristics of the cervix without entering the endocervical canal, and to rule out adverse presenting parts such as placenta, umbilical cord, or fetal extremity. *Fifth*, the examining hand is supinated, the perineum is pressed backwards, and the middle finger is passed through the cervical canal in a direction perpendicular to the presenting part. *Sixth*, the Drew-Smythe catheter, with the stilette slightly withdrawn, is passed along the tunnel formed by the hand and other examining fingers, then through the endocervical canal guided by the middle finger. Contact with the wall of the vagina is to be avoided although the gloved hand should be soaked in antiseptic first. *Seventh*, the stilette is pushed home and the anterior amniotic cavity is entered rapidly along the guiding finger. The stilette is then pulled out and the tip of the catheter is carefully eased into the posterior cavity. *Eighth*, the stilette is fully withdrawn and the maximal amount of liquor amnii is drained off passively. The catheter may be gently moved if an obstruction is obtained. *Ninth*, the fluid is collected for measuring volume and inspecting for meconium. *Tenth*, the fetal heart is monitored during the procedure, more especially during fluid drainage. The operation will take less than a minute provided the fluid obtained measures no more than 2-300 ml. The objective is to drain as much fluid as practicable while minimizing the time spent in the dorsal decubitus. If hydramnios is suspected, the semilateral position should be arranged.

There were contraindications to surgical induction of labor:

- (a) when maturity was in doubt; a delay of 1-3 weeks is instituted for reassessment,
- (b) within 24 hours after external cephalic version,
- (c) if cord or limb was identified in the vaginal fornices at the time of vaginal examination for the purpose of induction (Kerr Grieve

noted that the cord or limb was often no longer palpable 24–48 hours later), and

- (d) if there were signs of vaginal trichomoniasis or candidiasis; in these cases induction might proceed after several days of chemotherapy.

Induction solely by oxytocin was virtually never used. Augmentation after initial surgical induction consisted of two International Units (2.0 IU) of oxytocin added to 500 ml of 5.0% dextrose in water, the equivalent of 4.0 IU per liter, or 4 mIU/ml. The rate of infusion was 10–40 drops/minute, or 2.7–10.7 mIU/min. These are rates of infusion and concentrations compatible with presently recommended usage. Infusion pumps were not available. Prolonged infusion was not often used at Motherwell, although the protocol allowed for infusion times which exceeded all concurrent recommendations (15 to 60 hours, for absorption of total infusions up to 2500 ml).

Oxytocin augmentation was used in 2,069 of the 10,665 surgical inductions, 19.4 per cent. The total doses given are summarized in Table 4-5.

Table 4-5
DELIVERIES AT VARIOUS TOTAL DOSAGES OF OXYTOCIN

Total dose	Patients	Per cent oxytocin cases
≤5 IU	1445	69.8
5.1-10.0	364	17.8
10.1-15.0	99	4.8
15.1-20.0	73	3.5
>20.0	88	4.3

These details of the Motherwell Protocol are provided so the reader will understand the base from which Kerr Grieve's data and reasoning has flowed. Other aspects will be discussed later in this chapter and book, in particular, on the birth weights achieved by the protocol (Chapter 6) and the effects the dietary regimen had on gestosis or preeclamptic toxemia (Chapter 5).

ABDOMINAL DELIVERY

The further details of Kerr Grieve's astonishing achievement on lowering use of abdominal delivery are of interest. They represent a powerful challenge to the liberal use of section delivery in the industrialized world today.

There were 15,820 births at Motherwell Maternity Hospital during the

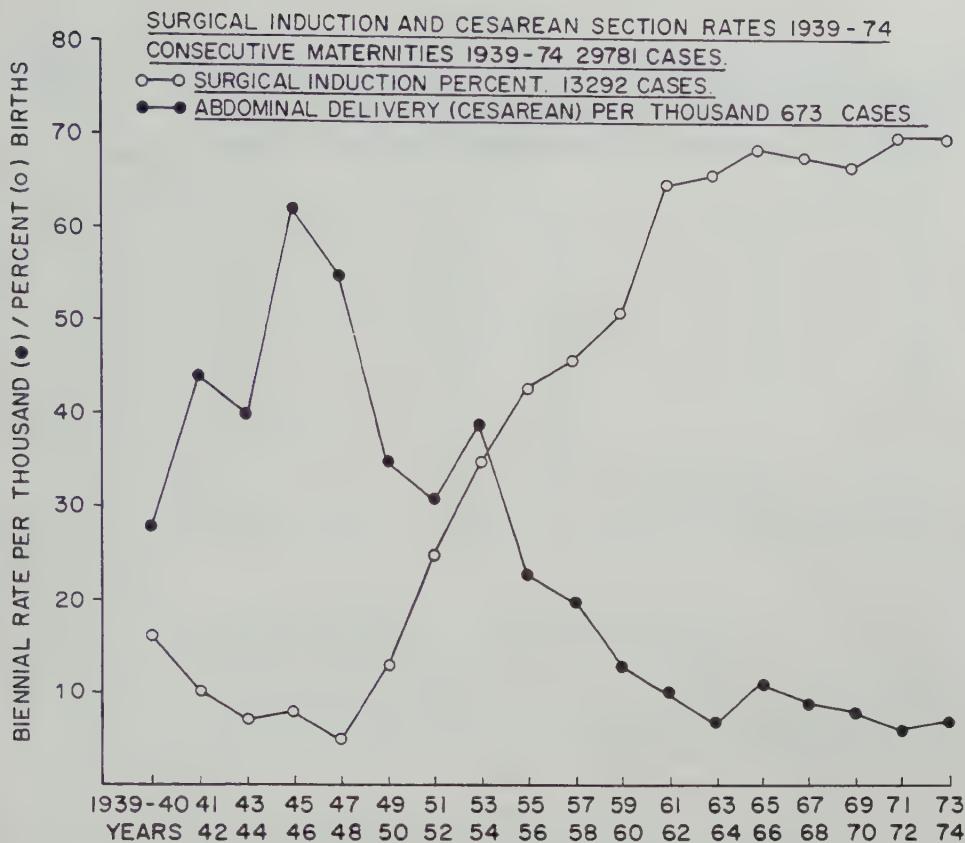


Figure 4-3. Surgical induction and section delivery rates, in 29,781 confinements, Motherwell Maternity Hospital, 1939-1974.

active Protocol. Five thousand one hundred and fifty five were *not* surgically induced. The clinical reasons varied: emergency admission, spontaneous onset of labor prior to scheduled initiation, doubt as to true state of maturity, known placenta previa, and failed appointment. All of these situations, and some minor reasons, led to 93 section deliveries ($93/5155 = 1.8$ per cent). There were more deliveries before 38 weeks in these cases, $1439/5155 = 27.91$ per cent, compared to the surgically induced group, $87/10,655 = 0.816$ per cent. This is a dramatic difference in its own right, with $\chi^2 = 3012$ (!), $p < < 10^7$. Actually, the difference is so great that the best conclusion, or perhaps better, the only conclusion, is that these results from the same obstetric institution came from vastly different universes of pregnant women. Nutritionally this is certainly true. Reconciliation of the overall section experience is in Table 4-6.

Table 4-6
RECONCILIATION OF 15,280 BIRTHS, 1960-76, CLASSIFIED BY MATURITY WITH
THE FREQUENCY OF PERINATAL DEATHS AND ABDOMINAL DELIVERY

Category	Surgical induction	Spontaneous labor	
	(87 at <38 weeks)	≥38 weeks	<38 weeks
Number out of 15,820	10,665 (67.4%)	3,716 (23.5%)	1,439 (9.1%)
Section delivery	36 0.3376%	55 1.48%	38 2.64%
Perinatal death	122 11.4*	74 19.9*	274 190.4*
Corrected for anomaly	57 5.3*	38 10.3*	180 125.1*
Perinatal deaths after section	2	5	9
Perinatal deaths per 100 sections	5.55	12.73	23.68

*Rates per 1,000 live births.

The dietary reinforcement of maternal health is reflected, remarkably, even in failed sections, that is, those with perinatal death as an outcome (the lowest segment of Table 4-6). The distribution of the 16 section related perinatal deaths, although small numbers, is significant: $\chi^2 = 6.5716$, $p = 0.0374$, 2 degrees of freedom (2 x 3 table). *Res ipsa loquitur.*

THE ABERDEEN UNIVERSITY REVIEW

Over the years, the obstetric care and the special diet became well recognized and accepted in the greater Motherwell area (the Burgh of Motherwell and Wishaw). This was in part true because effectiveness of the dietary program involved the continuing cooperation of the patient and her relatives and neighbors. Kerr Grieve invited Mary Campbell Brown, M.D., Ch.B. and Frank D. Johnstone, M.D., of Aberdeen University, to visit Motherwell in 1976, to interview and perform tests on samples of women in the protocol, and in general to assess the outcome of the program. This set into motion an assessment which lasted several years, with a report in the early 1980s. They found a difficulty, later experienced by the investigators at Research Triangle Institute in North Carolina (Chapter 6); namely, regional controls outside of the special program were in short supply. Brown and Johnstone faced a vastly different analytic problem as well, the plethora of recorded information, which I experienced ten years later in trying to encompass the record. Their report back to Kerr Grieve was based on testing contemporaneous pregnancies and reviewing selected subjects for various points.

Table 4-7
COMPARATIVE MEAN DAILY DIETARY INTAKE

	<i>Department of Health</i>	<i>Aberdeen outpatients</i> ¹	<i>Motherwell outpatients</i> ¹	<i>Motherwell inpatients</i> ²
Gestational age (weeks)	<14	14-40	23-32	32-40
Number	-	-	140	18 ³
Energy megajoules (kcal)	9.2 ⁵ (2200)	10.0 ⁵ (2400)	8.7 (2089)	6.0 (1443)
Protein g. (% total energy)	55 (10.0)	60 (10.0)	70.7 (13.5)	87.9 (24.4)
Fat g. (% total energy)	- (40.7)	- (47.9)	94.4 (45.4)	76.8
Carbohydrate g. (% total energy)	240.8 -	97.1 -	122.3 (46.1)	(26.9) (33.4)

¹ Mean of 7 days² Mean of 6 days³ All primigravidae⁴ One secundigravida, nine primigravidae⁵ See also Table 2-1 on the conversion from megajoules to kilocalories

Dietary intake in Motherwell was compared to a Department of Health Social Services survey in 1969 and to an Aberdeen University outpatient project (Table 4-7).

The choice of an Aberdeen sample as comparative control was further justified from a similarity in history and demographics. Both communities were urban Scottish with a settled population which experienced a period of relative prosperity for three decades after World War II. Social class attribu-

Table 4-8
SOCIAL CLASS DISTRIBUTION: A TEN PER CENT SAMPLE
OF ECONOMICALLY ACTIVE MALES, 1971 CENSUS

<i>Social class</i>	<i>Aberdeen city</i>	<i>Per cent</i>	<i>Burgh of Motherwell and Wishaw</i>	<i>Per cent</i>
I	221	4.51	85	3.83
II	665	13.44	247	11.14
IIIA	537	10.95	218	9.83
IIIB	1790	36.49	955	43.06
IV	1033	21.06	366	16.50
V	569	11.60	320	14.43
Other and unknown	96	1.96	27	1.22
Total	4905		2218	

Percentages do not add to exactly 100 per cent due to rounding.

tion, a feature of public statistics in Great Britain, was examined for 1971 from reports issued by The Registrar General for Scotland (Table 4-8).

The table shows the demographic profiles of northeastern and southwestern Scotland to be closely similar. The three "lower" classes (IIIB, IV, V), proxies for economic status, total 73.99 per cent in the Burgh of Motherwell and Wishaw and 69.15 per cent in Aberdeen City, indicating a few more women of lower economic status in the population of The Motherwell Protocol. Of more direct importance to the results of the study were certain physical characteristics of the mothers (Table 4-9).

Table 4-9
MATERNAL CHARACTERISTICS AND PREGNANCY OUTCOME,
ABERDEEN CITY (1968-70) AND MOTHERWELL (1976)

<i>Characteristic</i>	<i>Inpatients</i>	<i>Motherwell Outpatients</i>	<i>Aberdeen City Primigravidas</i>
Number	10	18	2043
Maternal weight at 20 weeks (kg)	56.1 ± 6.8 ^a	58.1 ± 8.5	60.2 ± 8.5
Maternal height (cm)	161 ± 4.2	161 ± 5.3	159 ± 5.8
Mean weight gain per week, 20-30 weeks (kg)	n.a.	0.26 ± 0.16	0.49 ± 0.21
Mean weight gain per week, first to last prenatal visit (kg)	n.a.	0.22 ± 0.12	n.a.
Birth weight (g)	2989 ± 246	2958 ± 295	3393 ± 415
Gestational age (weeks)	38.9 ± 1.2	38.6 ± 1.5	n.a.
Antenatal care (weeks)	23 ± 6.1	25 ± 4.1	n.a.
History of smoking (per cent)	40	39	39

^a N = 9 for this datum; all data are means ± standard deviation.

Although the table highlights lower birth weights from the Motherwell pregnancies, these are representative of the Protocol at large (see Chapter 6).

Brown and Johnstone undertook studies of nitrogen retention in Motherwell gravidas and noted some variation in actual compliance with the objectives for protein intake through consumption of meat as outpatients. This, of course, was well observed and accounted for by Kerr Grieve by diet success ranking. Brown and Johnstone performed 24-hour urinary nitrogen indices on ten inpatients at Motherwell Maternity Hospital and just ten of the larger sample of Motherwell outpatients (Table 4-10).

Brown and Johnstone provided several observations with their summary. The first was that first day indices would reflect the home environment but by the fifth day, inpatients would have adapted to the new circumstances. By contrast, the outpatient study would retain the vagaries of the domestic circumstances. This is seen in the data in Table 4-10. The second was that the Aberdeen caloric intake was closer to the level recommended by the

Table 4-10
TWENTY-FOUR-HOUR URINARY NITROGEN INDICES
ON TEN INPATIENTS AND TEN OUTPATIENTS

Determination	Inpatients		Outpatients	
	Day 1	Day 5	Day 2	Day 7
Nitrogen intake (g)	n.a.	13.4 ± 2.35	15.8 ± 5.7	15.8 ± 5.7
Urine volume (ml)	1122 ^a ± 343	1395 ^a ± 382	1253 ± 382	987 ± 528
Urine nitrogen (g)	8.1 ^c ± 1.7	12.5 ^c ± 3.1	9.9 ± 3.0	8.4 ± 2.7
Urea/Creatinine (g/g)	7.3 ^b ± 1.2	8.5 ^b ± 1.2	8.5 ± 1.8	7.4 ± 1.8
Creatinine (g)	0.93 ^b ± 0.18	1.25 ^b ± 0.22	1.00 ± 0.18	0.84 ± 0.23

^a p<0.05; ^b p<0.01; ^c p<0.001

Department of Health. The Motherwell energy intake was about 30 per cent less, despite affirmations by Motherwell dietitians that the women were not urged to reduce intake, just as to the mix and variety of foods. More specifically, the energy intake obtained from carbohydrates and fats in Aberdeen came to 1813 kcal and in Motherwell, 1117 kcal. The difference, 696 kcal, is 38.38 per cent of the Aberdeen diet. This is, of course, a substantial difference. Other research from Aberdeen had indicated urinary nitrogen indices would reasonably reflect nitrogen intake over the previous few days [270].

Inpatients showed a significant increase in all four indices by the fifth day (Table 4-10), with high correlation between nitrogen content and excretion ($r = 0.781$), which compares favorably with a similar study in 21 primigravidas from Aberdeen ($r = 0.792$) who also did well on daily nitrogen intake, 12.5 g, with a daily urinary nitrogen output of 10.2 g. In their internal report to Kerr Grieve, Brown and Johnstone noted the Motherwell women were a strongly motivated group, apparently more so than Aberdeen primigravidas generally.

By another perspective, the rapidity of the change for Motherwell inpatients is collateral evidence for the lack of a storage pool of amino acids in protein metabolism [459], despite the evident need to adapt to a higher, more consistent intake [131,425]. By contrast, the outpatient values indicate a higher efficiency for nitrogen retention and less change over the interval, attributed to their familiarity and expertise with the diet protocol after a trimester of experience. The correlation for the whole group was 0.908 ($p<0.001$), with a slope of 0.74 g/g intake. This indicated, to Brown and Johnstone, that *the body had not yet reached the limit of its absorptive capacity for protein*. Thus, despite variations in diet success, the Motherwell protocol did

supply protein for the structural needs of fetal growth and uterine preparation for labor in most cases, despite lower energy intake, with slowing of intrauterine growth rate by comparison with Aberdeen outcomes.

The prevailing paradigm states that enhanced birth weight is the essential *raison d'être* for both prenatal care in general and for nutritional supplementation in particular. Yet, here we have good evidence on a broad scale that high protein: low calorie diets provide *no less well* for both mother and infant than higher energy intakes compounded by a markedly increased use of abdominal delivery as a surgical exercise. This is a modest conclusion which in reality is actually stronger if one concludes that strengthening the uterus for responsiveness to stimulation of labor is a better outcome than encouraging section deliveries. Comparative controls from the Burgh of Motherwell and Wishaw, not subjected to the Kerr Grieve program, had more perinatal deaths in general (Table 4-6), more perinatal deaths attributed to anomaly (130/5,515, 2.36%; protocol cases, 65/10,665, 0.61%; $\chi^2 = 93.2456$, $p < 0.00001$), and more perinatal deaths from failed section deliveries (as noted above). Surely these are better outcomes for the infant.

MacGillivray [346] acknowledged the high protein, relatively low energy Motherwell diet resulted in lower birth weight infants (which were healthy) but asserted the parallel question on prevention of gestosis could not be answered from Kerr Grieve's work because of the lack of a control group. Here, MacGillivray missed the point that the Motherwell Protocol did have controls at two levels: (1) from within the community at large, as described above, and (2) by stratification of diet success, the degree of adherence to the Protocol itself.

The question of risk for the development of gestosis was expressly undertaken by Kerr Grieve. The results indicate a considerable reduction in prevalence of all types of gestosis, and in a manner which shows their significant relationship to diet. This is examined in further detail in Chapter 5.

Kerr Grieve did not provide an overall birth weight analysis; rather, due to the enormous amount of data, his lengthy summary has infant birth weight outcomes for various subsets of the protocol including a select sample of young primigravidas, a complete analysis of elderly primigravidas, and twins. These are discussed in more detail in Chapter 6. The protocol also resulted in favorable changes in the prevalence of mental handicap, including Down syndrome. This is discussed in more detail in Chapter 7.

Chapter 5

PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL EFFECTS OF MALNUTRITION

MALNUTRITION AND IMPAIRED BRAIN DEVELOPMENT

THE MEDICAL PHENOMENA underlying the direct link between irreversible brain damage including permanent brain underdevelopment, which commonly afflicts the low birth weight child, and maternal nutritional deficiency become more lucid when one recognizes that brain development occurs exponentially during pregnancy [357,566]. From conception, fetal development is so rapid that if an adult continued to grow at the rate of late fetal growth throughout life, he would be substantially larger than the size of the earth [52]. Especially important during fetal growth is formation of the brain, which is developed more during the fetal stage than any other organ [555]. The complexity of the nervous system almost defies analysis, but approaches to cell systems in lower forms of animal life have indicated the proper direction [281].

Maturation and cellular growth involve both cell hyperplasia and hypertrophy [422,495,565,569]. Malnutrition, although retarding both processes, is most pernicious during periods of rapid hyperplasia, that is, cell division [565,569]. Brain cell division, which peaks approximately one month before birth, stops in the main at approximately eighteen months of life [565]. Most brain growth after five months of age, when cell division levels off, results primarily from further growth of individual cells (hypertrophy) [557,565], plus the spread of neural connectivity.

The head circumference of a newborn infant is approximately 60 to 65 percent of the fully developed adult head circumference [39]. The brain of a one-year-old child weighs approximately 70 per cent of the adult [514], and

that of a four-year-old child is 90 per cent of adult size [495]. This enhanced early growth is termed *cephalization*; the rest of the human body catches up to and then exceeds brain growth, but only over the next 15 to 20 years.

Inadequate nutrition, especially from midpregnancy to five months of age, when the number of brain cells rises to about 80 per cent of the adult, can result in a permanent deficit of or damage to brain cells [39,114,495,565]. During the most rapid period of brain development, from the last trimester of pregnancy to the first month or two of life, malnutrition can cause irreversible neurological damage and permanent brain underdevelopment [39,422,495]. After the age of two, poor nutrition basically retards the growth of individual brain cells, resulting in mental deficiencies which are more likely to be reversible [422].

Effects of preeclampsia on some of these parameters have been reported, reductions in head circumference, birth weight, and placental weight [130]; it seems likely these are mediated through gestational dysnutrition.

In an analysis of the brain tissue from 31 humans, Winick demonstrated that brain size, as measured by brain RNA, protein, and weight, increases roughly linearly from 13 weeks of gestation to age 13 months post natal (in order to minimize decomposition, all brains were examined within one hour after death.) However, the study also showed that the number of brain cells, as indicated by DNA content, increases in near linear fashion until six weeks postnatal and then levels off. At the age of six months, brain DNA is close to the adult level. Hence, after birth, there is a marked increase in RNA and protein per brain cell, accompanied by a decline in the proliferation and growth of brain cells [565,569].

During at least the first few months of life, malnutrition does not appear to affect appreciably the amount of protein or RNA per brain cell [569]. However, as mentioned, it does markedly reduce the number of brain cells. A study identified three infants dying as a result of malnutrition, all under 2,000 g at birth, which had only 40 per cent of the brain cells as the better nourished infants of the same age [569].

In the same study, brain weight, and protein, RNA, and DNA levels of nine infants, between two weeks and eleven months of age, dying from malnutrition (triangles, Figs. 5-1 through 5-4), were compared with the same measures of brain development to two fetuses from therapeutic abortions and eight infants dying accidentally (circles, Figs. 5-1 through 5-4). The number of brain cells, as measured by DNA, was significantly lower in malnourished subjects; the amount of RNA and protein per brain cell was comparable in the two groups. In Figures 5-1 through 5-4, the paired lines represent the range for normal children in the United States. The other subjects were Chilean [569].

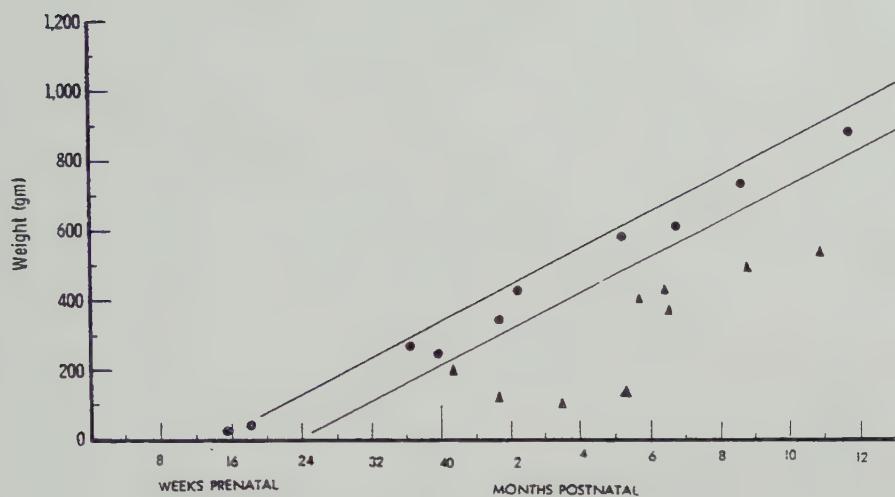


Figure 5-1. Effect on brain weight

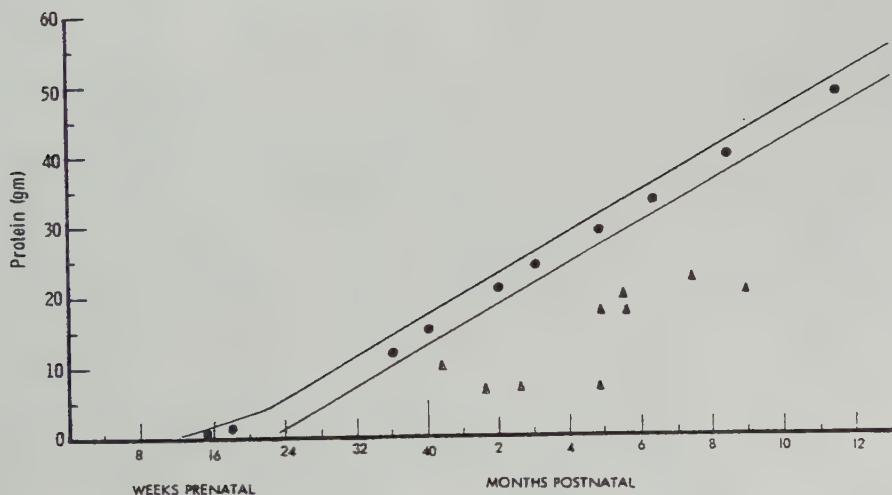


Figure 5-2. Effect on brain protein. (Figures 5-1 and 5-2 courtesy of M. Winick and R. Rosso: The effect of severe early malnutrition on cellular growth of human brain. Circles within paired lines, normal controls. Triangles, malnourished infants. *Pediat Res*, 3:181-184, 1969).

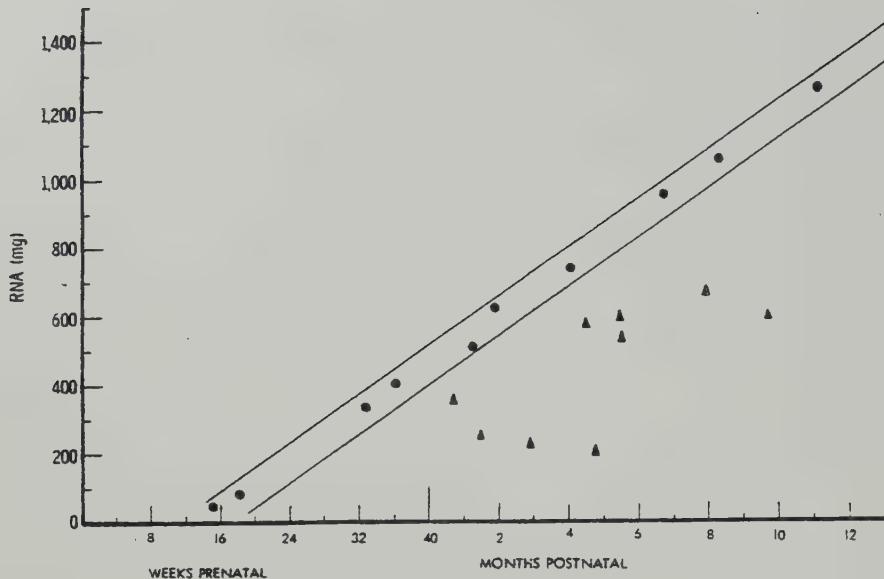


Figure 5-3. The effect on brain RNA.

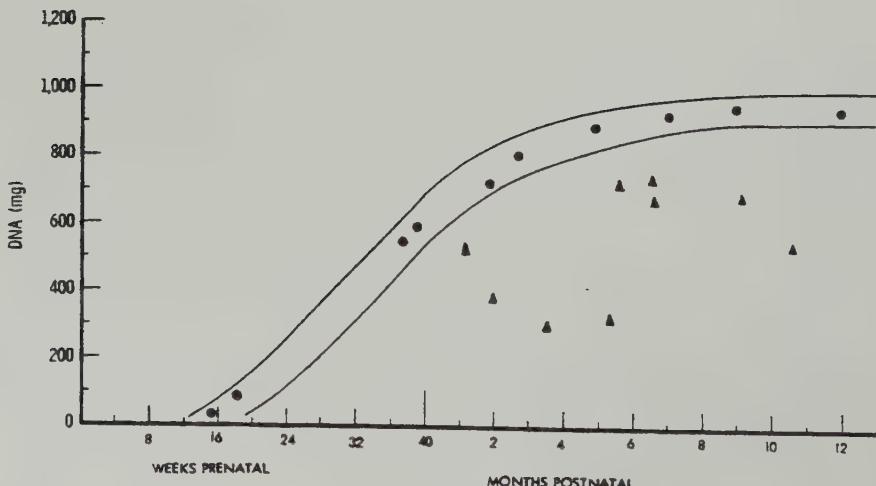


Figure 5-4. The effect on brain DNA. (Figures 5-3 and 5-4 courtesy of M. Winick and P. Rosso: The effect of severe malnutrition on cellular growth of human brain. Circles within paired lines, normal controls. Triangles, malnourished infants. *Pediat Res*, 3:181-184, 1969).

Because brain development is accompanied by three major growth spurts, it is selectively vulnerable to malnutrition at different stages [139,495]. Neuronal growth from the 18th to the 28th week of gestation is characterized by rapid proliferation [139]. All of the roughly 11 billion neurons, which process and analyze neurochemical and electroneural information, are formed before birth [495]. The second major growth phase is glial multiplication [139], which occurs between the 20th week of gestation through to at least two years of age [322], although most glial proliferation is completed by age one [139,260]. Glial cells, which form and maintain the myelin sheaths, set the foundation for a major part of neurological development, myelination, which continues up to about age four years [56,260].

Malnutrition at various stages retards neurological development. Especially after midpregnancy, it causes a reduction in the number of glial cells [139], the proliferation and growth of which are more vulnerable to malnutrition than any other cell in neurological development [322]. Poor nutrition during infancy can reduce the size of a glial cell [39]; during childhood, it retards myelination [139]. A decrease in the number of glial cells and insufficient myelination affect intelligence, but perhaps not as significantly as other forms of brain development, which occur concurrently with and are dependent on glial multiplication and myelination [139]. Impairment in the formation and development of dendrites may affect learning ability more than a reduction in the number or size of brain cells. The number of dendrites and connections (synapses) is the most critical aspect of the process which is nutrient dependent [260].

It is important to not oversimplify what must occur for fully normal brain structure and function to be put into place. Integrated brain architecture is a hierarchy of regions, domains, layers, interconnections, multiple cell types, structural proteins, cell receptors (proteins), and specialized synaptic proteins (e.g., synapsin I) which regulate neurotransmitter release through phosphorylation [494]. We have to allow for further departures from simplicity given the current state of our awareness of these matters.

The interneuronal network is formed basically during the first two years of life [93,94,260,322]. While the connections between neurons are markedly affected by malnutrition, the precise relationship is difficult to quantify. The size of axons, which comprise a major part of the total nerve mass, is known to be stunted by intrauterine and early postnatal malnutrition.

The cerebellum is largely developed between the 30th week of gestation well into the first year of life, during which time the organ shows marked cell proliferation. Thus, the cerebellum is more vulnerable to malnutrition during this interval [93] than the cerebrum [89], which develops over a longer period [139].

Hence, malnutrition during critical stages of brain development causes changes in size, electrical activity, composition, and morphology of the central nervous system [422]. Neurohormones, which mediate nerve impulses between nerve cells, are reduced in quantity by inadequate nutrition. One researcher, who demonstrated that fetal malnutrition leads to aberrations in perception, short attention span, apathy, instability, impairment of perceptual-motor integration, and abstract reasoning, theorized that mental function is related more to the development of interrelationships between the senses than to the development of individual senses [38]. It was noted that inadequate nutrition leads to impaired intersensory integration [39].

Perhaps as common a precursor of mental deficiency, possibly a more likely event preceding epilepsy than deficiency of brain cells, is a lesion called periventricular venous infarction [532]. Anoxia, or hypoxia, are poorly understood processes, despite the common belief they are simply the result of oxygen deprivation, partially or wholly. The parallel situation of genetically determined anemia, such as congenital spherocytosis, which can manifest in newborns as well as during infancy [541], reminds us that brain injury can be quite indirect. The mechanism in congenital spherocytosis depends on erythrocyte hemolysis and hyperbilirubinemia, leading to kernicterus [541]. Deficiency anemias undoubtedly have an effect through requisite vascular adaptations which follow contraction of fetal blood volume. Such lesions could be a terminal effect of maternal malnutrition.

Periventricular venous infarction, a common fetal or neonatal lesion often found in premature infants, has been well described [25,520,532]. If this were a preventable lesion, the associated neurological morbidities, such as epilepsy, cerebral palsy, behavioral disorders, and mental retardation, would occur less often [520].

Shneour, in a well-documented monograph, clearly demonstrated that impaired cognitive potential, which the author asserted was still widely believed in 1974 to be causally related to race, is basically caused by malnutrition [495]:

In this country, major biomedical efforts have pinpointed a number of fatal diseases for eradication, including poliomyelitis, cancer, and cardiovascular disorders. There has been a particular emphasis on diseases that affect children, and the news media often report cases that elicit immediate and generous response from individuals and organizations. But the oldest and most persistent scourge of mankind, which most often affects children and destroys their life opportunities – the triad of hunger, poverty, and ignorance – is largely forgotten by the community . . . one would assume that medicine devoted to the care of women and children would be the most advanced part

of medical research and practice. Yet nothing could be further from the truth . . . why is there so much indifference to this subject of hunger, malnutrition, and starvation, when children and pregnant women, who generate instinctive sympathy and concern from almost everyone, are the most severely affected victims? [495]

MALNUTRITION AND PLACENTAL PATHOLOGY

The fetus is basically nourished through the placenta, which is bathed in maternal blood and conveys fetal blood. Two common forerunners of what is called fetal anoxia are believed to be nutrient deficient maternal blood and placental dysfunction, both of which may be direct results of malnutrition. The consequences of the former as a cause of *anoxia* will be discussed later.

Malnutrition causes a deficiency of cells in the placenta [176,312,568], which normally has completed cell proliferation about 35 weeks of gestation [176,312,483,565,568].

It has been said this cell change triggers the placenta to form vasoconstrictor substances as a compensating mechanism to improve placental blood flow and alleviate poor uteroplacental nourishment [176]. Blood pressure frequently increases as a consequence of this compensatory process. The basis for this concept would seem to be that vasoconstriction elsewhere in the blood vascular system would enhance uterine flow, an idea very different from what is meant by the physiological term *hemometakinesia*. To the contrary, as shown by Kerr Grieve and, more recently, by Rosso [461], pregnancy is more a volume control scenario than a pressure regulatory process.

Two independent studies of single births by Lechtig et al. have shown that inadequate maternal nutrition leads to an abnormally small placenta [312]. This work was an addendum to a supplementation study in four Guatemalan villages [309-313]. The placentas of 29 pregnant women in two villages receiving a protein/calorie supplement were compared with the placentas of 27 women in two other villages who received another supplement which contained approximately a third the calories of the first supplement. The calorie supplement had nearly the same amount of vitamins and minerals as the protein supplement but had no protein. As set by the design of the study, there were no significant differences in height, parity, age, sex of child, socioeconomic status, length of gestation, morbidity during pregnancy, or caloric intake other than the special supplements by group. A further implicit control was the absence of any type of self selection, due to the extremely isolated, rural nature of the program.

Placental weight was significantly higher among women in the four

villages who received any supplement, regardless of whether protein was supplemented. The additional protein in one of the supplements had no significant effect on placental weight. This apparent paradox is probably attributable to the fact that the supplementary protein, which was derived from a corn-based cereal, was lacking in one or more essential amino acids or possibly the women were deficient in calories [312]. Platt has shown that even a diet adequate in protein, if deficient in calories, can lead to protein deficiency, since some protein is utilized for energy rather than for tissue synthesis [405,422]. This may well be a matter of debate, given the results of the Motherwell Protocol, but as will be discussed, the total nutritional milieu has to be taken into account. This was shown forcefully by Prentice and associates in studies of nutritional supplements to rural women in Gambia [425,427-429]. They found that supplements were not effective in the dry season because they added little to the effective primary intake of women during pregnancy but the same supplements were extremely effective in the wet season. This is discussed further in Chapter 6.

The major finding from Lechtig et al. [312] was an increase in the average placental weight, 11 per cent, for women receiving at least 20,000 supplemental calories during pregnancy compared to women receiving <20,000 additional calories [312]. However, the placental concentrations of protein, water, hemoglobin, or DNA were not affected by caloric supplementation.

In a parallel study, the authors compared the placental weight of 19 high socioeconomic status women with thirty who were said to be of low socioeconomic status, as determined by the family income, the educational level achieved by the mother, and environmental sanitation. The comparison was further controlled by the exclusion of female newborns, multiple pregnancies, primigravidas, and those with more than three previous deliveries. The mean annual family income was \$9,600 in the former group and \$500 in the latter (1975 dollar values). As expected from study design, two groups of women, all residing in the same urban area, were found to be similar in age, parity, and length of gestation. In addition, women were excluded if they had severe intercurrent disease during pregnancy [309-313].

Even though women with a severe disease (which would tend to occur more among women in the low socioeconomic status group with a lower placental weight) were excluded and the length of gestation, also associated with both low socioeconomic status and low placental weight, was controlled, the average placental weight was 15 per cent lower in the group of low income women than in the group of higher income gravidas ($p<0.01$). As in the former study, the researchers found no difference between the two groups in placental concentrations of protein, water, hemoglobin, or DNA. However, the concentration of fat was definitely lower in the low socioeconomic pregnancies

($p<0.05$). Perhaps the most revealing finding was that placental weight was highly correlated with the surface area of the placental peripheral villi ($p<0.01$), which largely determines the efficiency of nutrient transport [312].

Pooling the data from both the urban and rural studies, the authors showed that placental weight and birth weight were correlated at the 1 percent level of statistical significance. This reasonably high degree of association, which was not affected by controlling for either socioeconomic status or the amount of added calories, confirmed previous findings by Hytten and Leitch [96]. The conclusion from the Guatemalan studies was that maternal malnutrition caused low birth weight primarily because of its effect on reducing the size (and presumably the functions) of the placenta.

The Collaborative Study of Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Childhood (Collaborative Study) showed a very high association between low placental weight and low birth weight and perinatal mortality [402] (Tables 5-1 and 5-2).

Perinatal deaths were found to have a complex relationship to placental weight which was more striking than a few differences in the rates when examined between whites and blacks. The following remarks are based on consolidation of the data into a whole [402, p. 448]. Most births with placentas weighing less than 200 grams resulted in a perinatal death (86.48 per cent); the rate then falls progressively and dramatically across the placental weight spectrum up to 599 grams, and then rises again, when viewed in four subsets (Table 5-1).

Table 5-1
PERINATAL DEATH RATE BY 200 GRAM
INCREMENTS OF PLACENTAL MASS [402, P. 448]

<i>Placental weight groups (grams)</i>	<i>Total births</i>	<i>Perinatal deaths</i>	<i>Per cent perinatal deaths</i>
0 - 199	318	275	86.48
200 - 399	11,387	449	3.94
400 - 599	19,088	217	1.14
600+	1,771	47	2.65

An important factor behind this hyperbolic relationship is that heavy placentas are often the result of severe, largely disseminated disorders. Similarly, placentas weighing less than 200 grams are almost entirely from very premature deliveries. Thus, the seemingly extraordinary difference between placentas below 200 grams and those weighing from 200 to 399 grams is in part a statement on gestational age. Niswander and Gordon [402] did not provide either: (1) simultaneous analysis of gestational age and placental weight or other paired factors such as Hardy et al. [229] reported

later in their analysis of developmental and neurological factors, or (2) the raw data by which to undertake the necessary calculations. Hardy et al. [229], in the course of their many two-way analyses, automatically reported the raw data by which their calculations could be verified. The result is also, in part, an artefact of the choice of group ranges. The result is muted when smaller increments are applied, revealing a sigmoid pattern with a small rise in perinatal mortality for placental weights >500 g. The latter is of dubious significance; it would be better to conclude, biologically, that perinatal mortality attains a low plateau of minimal risk when placenta weight is ≥ 475 grams.

The rate of change across the span of placental weights from 200 to 399 grams, a range of 200 grams, can be assessed from columnar data provided by Niswander and Gordon, with further contrast from even smaller placentas [402] (Table 5-2).

This shows, if plotted graphically, exponential decay heightened by the results from placentas under 200 grams (Table 5-2).

Table 5-2
PERINATAL DEATH RATE BY 50 AND 100 GRAM INCREMENTS
OF PLACENTAL MASS UP TO 400 GRAMS [402, P. 448]

<i>Placental weight groups (grams)</i>	<i>Total births</i>	<i>Perinatal deaths</i>	<i>Per cent perinatal deaths</i>
0 - 99	33	33	100.00
100 - 199	285	242	84.91
200 - 249	374	132	35.29
250 - 299	1,192	112	9.40
300 - 349	3,616	107	2.30
350 - 399	6,205	98	1.58

An artificial picture can be drawn by selecting subsets at particular swing points along the curve. For example, among births with placental weights between 200 and 399 g, the prevalence of perinatal death was 3.87 per cent; for births when the placenta weighed between 400 and 599 g, 1.16 per cent died perinatally. This latter difference has been calculated as significant at the 10^{-10} level. The difference, as large as it is, is artificial because the progressive larger relationship between placental weight and perinatal mortality is not linear. The allocation here (as reported in the first edition) contains placentas weighing between 200 and 249 grams with an attendant perinatal mortality of 35.29 per cent. Likely more significant in biological terms was the relation found between placental weight and low birth weight, despite the tendency for relative collinearity. Low birth weight accounted for 22.64 per cent of births in which the placenta weighed 200 to 399 g; among those in which the

placenta weighed 400 to 599 g, it was 3.164 per cent; by contrast, for placental weight over 500 g, low birth weight infants accounted for only 0.46 per cent. These data indicate the likelihood that placental weight is not related to birth weight is infinitesimally small.

Placental pathology, which sometimes leads to fetal and neonatal morbidity and mortality, is not known to be caused by hypoalbuminemia. Fibrinoid, commonly deposited in the placenta, often wrapped around placental villi, contains maternal albumin[70,71,379-381]. Protein/calorie deficiency impairs hepatic synthesis of albumin [56,278] and other coagulation factors found in placental fibrinoid. Confluent fibrinoid can be so extensive as to result in severe fetal growth retardation [214,485].

In addition, deficiency of the B vitamins and other nutrients will impair hepatic detoxification of the large amount of estrogen, progesterone, and other steroids produced by the placenta through a reduction in hormone binding proteins synthesized [269]. Hence, inadequate nutrition leads to hepatic dysfunction [55,56,256], which may precede actual gross placental pathology. It is of great interest that hepatic storage of many nutrients, including albumin, is significantly related to birth weight [257].

Another consequence of malnutrition is a reduction during late pregnancy, and for a short period after delivery, of urinary estrogen excretion, possibly signifying an inadequately functioning placenta [258]. Maternal nutrition does not appreciably affect urinary estrogen excretion until after approximately the 32nd week of gestation. Birth weight and estrogen excretion at term, both indicators of placental function, are highly associated [258].

Numerous studies have shown that placental dysfunction, reduction of size, infarction, or malformations are associated with spontaneous abortion, stillbirth, low birth weight, prematurity, and complications of pregnancy [239,485]. Structural changes of term placentas are often pronounced when the mother had pregnancy related complications.

Extensive series of sequential fresh placentas shows the frequencies of infarction in premature labor is clearly lower than at term [484]. Cases of extreme fibrinosis or mixed infarction with fibrinosis are seen often in intrauterine growth retardation [211,485]. These cases emphasize the great reserve of the placenta, estimated at 0.33 to 0.50 of the whole from the range of placental:fetal weight ratios of "normal" births [484]. The essential lesion, given the commonly focal nature of most placental infarcts, is more likely ultrastructural or enzymatic and related to transfer mechanisms or perfusion pattern, so elegantly studied by Longo [338].

Accordingly, the risk for and pathogenesis of placental infarction must be through specific pathophysiologic processes, and not accorded significance

by a change in overall placental mass.

Most recently, the possible role of placental cytokines in gestosis has been explored [444]. Briefly, tumor necrosis factor, interleukin 1 β , and interleukin 10, all implicated in endothelial dysfunctions of gestosis, are expressed excessively [444].

Refining their data, Hepner and Bowen explained even after exclusion of the most functionally impaired placentas, i.e., those of infants with major anomalies or who were premature, infants with abnormal placentas showed signs of protein deficiency [239]. They compared 87 white, full-term infants (no congenital anomalies) associated with placental variations with a control group of 183 newborn infants with normal placentas. Many study infants, but not controls, experienced colic and "behaved as if starved."

At age six months, the 87 infants had outgained the control group infants by 810 g and retained 107 mg more nitrogen and 2.0 g more protein per day (based on arithmetic differences between the groups) over the controls. Among six-month-old infants of the same birth weight, index cases had outgained the control group by a total of 1,350 g and retained 178 mg more nitrogen and 3.3 g more protein per day. These results were attributed to "favorable variations" in placental function able to provide for nutritional needs, especially protein requirements. This was their way of expressing organ efficiency. Larger differences would have accrued if the premature and malformed infants, those most likely to be malnourished in utero, had been included. Nevertheless, Hepner and Brown concluded placental abnormalities are related to increased protein requirements and may themselves cause impairment of the efficiency of the utilization of ingested protein.

CONSEQUENCES OF SODIUM DEFICIENCY

Placental perfusion is compromised by hypovolemia, which inevitably results from sodium deficiency often with other dietary inadequacies. Because of hypovolemia, a deficiency of even one essential nutrient, such as sodium, can lead to placental infarction and reduced or retarded cellular growth [448]. In a study of 2,019 pregnancies, women who were told to restrict their salt intake were 2.5 times more likely to have an infarcted placenta than women who increased their salt consumption ($p<0.005$) [448]. Other than advice about sodium intake, there was no dietary or medical intervention in the study. The average placental weight was 608 g for the women on high salt diets compared to 592 g for those who decreased their salt intake.

The significance of this difference is ambiguous if real at all. The figures reflect immediate postpartum "fresh weights" and do not account for great

variations in the volume of trapped maternal blood. A "normal range" of fresh placental weights from a population with a 6 to 9 percent incidence of "toxemia of pregnancy" was 311 to 930 g with racial differences in the means: whites, 513.7 ± 8.9 g; blacks, 483.0 ± 8.1 g [483]. Later studies revealed as much as 20 per cent weight loss in specimens followed for up to eighteen to twenty-four hours postpartum [485]. This loss was due to the maternal blood seeping from the cotyledons. This observation makes a comparison of placental weights immediately after birth difficult at best.

Additionally, much of the placental weight data are uncontrolled for membranes and for remnant cord length [485]. That there is a relationship between fetal growth and placental mass as an index of capacity to function is undeniable. What has not been shown is the character or qualitative nature of the relationship.

Various dramatic physiological and biochemical adjustments, particularly hormonal changes, accompany pregnancy [159]. One such major adjustment is an increased retention of sodium (the principal electrolyte of the extracellular fluid compartment which consists of plasma in the blood vascular system, lymph, and the extravascular interstitial fluid) associated with expansion of these compartments [419,421]. Since numerous physiological changes accentuate sodium depletion, the requirements for dietary sodium, the cation of common salt, increase during pregnancy. Because expansion of the intravascular and interstitial extravascular compartments are crucial to successful pregnancy, a discussion of sodium metabolism is warranted. Obviously, to maintain the physiological extracellular water volume for adult women of reproductive age, which ranges from 0.193-0.256 liter/kilogram body weight (mean = 0.227 L/kg) [384], as weight is added (plus the newborn which has a water compartment nearly twice that of the mother, 0.439 L/kg [187]) some means has to be found to conserve the sodium the woman has at the start of pregnancy and to add to it appropriately. This very necessary change can be defeated by dietary restrictions, electrolyte depleting drugs, or both, through sodium depletion.

Progesterone secretion increases to 10-100 times the level in the non-pregnant state [331]. This is coupled with the hemodilution of volume expansion (hypervolemia) and reduced serum osmotic pressure due to the dilution of serum albumin concentration. This new vascular state greatly increases the potential for sodium excretion [333,480]. In addition, the glomerular filtration rate increases more than renal plasma flow, increasing the amount of filtered sodium at the renal tubule [480]. Progesterone, coupled with decreased serum pressure, augments the possibility of sodium depletion.

Depletion of sodium is prevented by a five- to ten-fold increase in aldost-

terone, which facilitates tubular reabsorption of sodium; this is the largest pregnancy renal adjustment [421,480]. The increase in aldosterone secretion is the last stage of the salt conservation mechanism (renin-angiotension-aldosterone homeostasis) [420], which maintains a near constant concentration of sodium in the extracellular fluid. As the potential for sodium depletion is created, the juxtaglomerular cells of the kidney synthesize renin, which prompts the release of angiotensin. Angiotensin II, formed by enzymatic action on angiotensin I, is the most potent pressor substance known [97]. In preeclampsia, although there is little change in the amount of plasma renin substrate (which increases three- to five-fold during normal pregnancy), plasma angiotensin II levels become markedly depressed.

Angiotensin, which increases in normal pregnancy up to ten times normal, stimulates the cells in the zona glomerulosa of the adrenal to secrete aldosterone [421], providing for tubular reabsorption of sodium. Increased activity of the renin-angiotensin-aldosterone system serves to retain sufficient sodium for the level of sodium in extracellular fluid to remain constant as the blood volume increases [421]. The degree to which sodium conservation occurs, even in normal pregnancy, is reflected by a five- to fifteen-fold increase in plasma renin activity [97].

Increased renin-angiotensin-aldosterone activity in a healthy, well-nourished gravida can be accompanied by physiological edema which goes beyond dependent collections in the legs or lower trunk. Retained sodium and water go from the vascular compartment to the extravascular interstitial compartment, forming edema. Increased aldosterone does not cause edema but may perpetuate it. However, this increased blood volume is benign, about 40 to 45 per cent above nonpregnant levels. Increased hormonal activity can cause edema [256]. Birth weights of infants of mothers with benign edema during pregnancy are, on average, higher than for infants of women who were not edematous. Although not all healthy pregnancies will be accompanied by edema, the sign of water retention in a healthy pregnancy generally reflects a favorable outcome (Table 5-3). Up to 80 per cent of pregnant women develop edema [446].

A feature of the renal regulatory mechanism of blood pressure, the medullipin sequence from the renal interstitial cells [388], has not been studied physiologically in human pregnancy although several pregnancies occurred in two women studied, but not reported as yet, by Muirhead, the principal researcher in this field [389]. One of these women had two pregnancies characterized by near total collapse of the placental intervillous space, the first requiring emergency section delivery for profound fetal distress. Further work may prove to be of great interest, given the marked hypotension seen in hypermedullipinemia [388].

One study of nonproteinuric women demonstrated that edema is associated with a 59 per cent reduction in perinatal mortality [96]. This change is significant at less than a 1 per cent level (Table 5-3).

Table 5-3
RELATION OF PREGNANCY EDEMA ON HANDS
AND FACE TO PERINATAL DEATH [96]

	Pregnancies	Stillbirths	Neonatal deaths	Perinatal mortality
No edema	2,268	33	40	32.19*
Edema	1,890	15	10	13.23*

*Rate per 1,000 births.

Edema, instead of being physiological, can develop paradoxically as a result of sodium deficiency, renal disease, infection, or protein and other dietary deficiencies [56]. In the case of protein or calorie deficiency (or both) the colloid osmotic pressure of plasma proteins is decreased by lower serum albumin concentration [487,515].

Strauss, by measuring the serum osmotic pressure of 65 pregnant women, all at seven months of gestation, demonstrated that the pressure was directly related to protein intake [515]. The average serum osmotic pressure among 35 nontoxemic women was 247 mm of water. More revealing, the serum osmotic pressure of twenty women with nonconvulsive toxemia was only 215 mm; that of ten eclamptics was 175 mm. As expected, both serum albumin and dietary protein intake were lowest among the eclamptics and highest among the 35 nontoxemic women.

Protein supplementation caused an immediate increase in the osmotic pressure of the plasma proteins. At the eighth month of pregnancy, 15 of the 20 nonconvulsive toxemics were placed on an extraordinarily high protein diet, 260 grams daily; the remaining five women were placed on an isocaloric diet with only 20 grams of protein. The osmotic pressure of the high protein group increased an average of 7 per cent; the osmotic pressure of the isocaloric, low protein group fell an average of 9 per cent.

A study of adult males, on an isocaloric diet low in protein but with adequate vitamins and minerals, confirmed Strauss: plasma albumin is directly related to protein intake [278]. After four to six weeks, hepatic synthesis of albumin fell markedly ($p < 0.05$).

The reduction in effective colloid osmotic pressure due to low plasma protein causes more water to be filtered out of the capillaries than is returned to them [487,515]. This imbalance results in edema much of the time. Not all protein deficient women become edematous, since as much as 6.67 kg of

excess water can be retained before edema is developed [487].

Of the four compartments of body protein (circulating plasma, labile reserve, dispensable reserve, and indispensable fixed), the plasma proteins do not undergo depletion until much of the labile reserve and dispensable reserve proteins are drawn down [487]. There are no recognizable manifestations of protein deficiency until plasma protein begins to be depleted. Hence, a pregnant women on a somewhat inadequate diet may, as a consequence, give birth to a mentally impaired infant without exhibiting clinical signs of protein deficiency. Our present diagnostic armamentarium has no means by which to detect this particular pathophysiologic state.

Even though sodium facilitates fluid retention, edema can also be a consequence of sodium deficiency, which causes a reduction in the flow of sodium to the distal tubule and a concomitant decrease in diuresis [421]. When dietary sodium is inadequate to maintain an expanded blood volume and increased extracellular fluids, the renin-angiotension-aldosterone mechanism is stressed in a futile effort to retain sufficient sodium [421]. The consequent increase in plasma renin activity may lead ultimately to a pathologically high activity of the juxtaglomerular cells [97]. Sodium deficiency inevitably leads to a decrease in circulating blood volume, which further stimulates the renin-angiotensin-aldosterone mechanism [420]. This vicious cycle is deemed a major contributory factor to gestosis (preeclampsia or metabolic toxemia, which ever is the reader's preferred term) leading to maternal and fetal pathology.

Sodium deficiency, from a low salt diet, diuretics, or both, leads to hyponatremia and hypovolemia [420]. Consequently, renal blood flow and glomerular filtration rate decrease. The extra stress on the salt conserving mechanism, coupled with decreased blood volume, leads to maternal complications, particularly toxemia of pregnancy, and intrauterine growth retardation. By reducing uterine blood flow, hypovolemia compromises placental perfusion and, consequently, fetal nourishment. As documented herein, fetal malnutrition is a common pathway to developmental disabilities.

Hypovolemia promotes an increase in renin secretion, which is frequently associated with increased blood pressure [419], a principal symptom of preeclampsia. Increased blood pressure, which is sometimes accompanied by edema (another symptom of preeclampsia), is probably a compensating mechanism for the reduced blood volume. This was the conclusion also of Kerr Grieve (Table 5-4).

This is clear enough: the better the diet, the lower the risk for unspecified gestosis, a rather impressive progressive relationship and distribution. The principal contention in studies of gestosis is whether E-gestosis (excessive

Table 5-4
GESTOSIS (ALL DEGREES) BY DIET SUCCESS GROUP

<i>Diet success level</i>	<i>Cases*</i>	<i>Gestosis</i>	<i>Per cent</i>
High	7559	28	0.37
Medium	2132	75	3.52
Low	5029	410	8.15
Very low	870	150	17.24

$\chi^2 = 830.17$, d.f. = 3, $p << 0.001$

*The number of cases may vary from one Motherwell table to another, using only those with complete information, unless otherwise specified. Tables 5-4 and 5-5 have the same group totals.

weight gain in pregnancy, usually due to fluid retention) is physiologic or pathologic, as discussed above. In his thorough way, Kerr Grieve recorded the subtypes of gestosis according to diet success group (Table 5-5).

The relationship between the Motherwell diet group classification and gestosis holds together when the limited form E-gestosis is considered. This says that some, if not most, of the edema seen clinically and provisionally qualifying as E-gestosis is in fact pathological and the result of poor nutrition.

Table 5-5
E-GESTOSIS DIET SUCCESS GROUP

<i>Diet success level</i>	<i>Cases*</i>	<i>Gestosis</i>	<i>Per cent</i>
High	7559	13	0.17
Medium	2132	30	1.41
Low	5029	151	3.00
Very low	870	33	3.79

$\chi^2 = 202.63$, d.f. = 3, $p << 0.001$

*The number of cases may vary from one Motherwell table to another, using only those with complete information, unless otherwise specified. Tables 5-4 and 5-5 have the same group totals.

Robinson, in an extensive study of over 2,000 pregnant women, demonstrated that sodium is an essential nutrient during pregnancy [448]. One thousand pregnant women were instructed to decrease their salt intake; 1,019 were told to increase salt consumption. Other than this dietary instruction on salt, the women were not given diverse dietary regimens or other medical advice. The two groups were of comparable age, parity, and socioeconomic status [448].

The rates of perinatal death, miscarriage, edema, toxemia, abruptio, and placental infarction were much higher among the salt restricted women. Assuming that diet was the only factor which resulted in lower rates of perinatal mortality, toxemia, and edema in the women with increased sodium intake (Table 5-6), the chance higher sodium intake did not reduce perinatal

mortality is about one in a million; that for edema and toxemia is much lower.

Table 5-6
CONSEQUENCES OF SALT RESTRICTION IN PREGNANCY [448]

	<i>Women</i>	<i>Perinatal deaths</i>		<i>Percentage occurrence</i>		
		<i>Number</i>	<i>Rate</i>	<i>Toxemia</i>	<i>Abruption</i>	<i>Edema</i>
Low salt	1000	50	50/1000	9.7	3.2	28.7
High salt	1019	27	26.5/1000	3.7	1.7	16.0

Despite the conclusive physiological, biochemical, and clinical evidence that sodium requirements increase during pregnancy, salt restriction, which was introduced more than seventy years ago on the pretense that toxemia is caused by impairment of salt excretion, was still widely advocated in medical practice in the 1970s [53,421]. It may well be less so today, but the continuing crisis of excessive low birth weight, premature onset of labor, and inflated use of abdominal surgical delivery gives one pause as to just how well the nutritional lesson has been learned *and acted upon*.

In reality, among toxemic women, salt retention is not a cause of the toxemia but an impending sign of sodium depletion [472]. Another reason the myth continues of sodium restriction as a means to prevent toxemia is that physiological edema is seldom distinguished from pathological edema. Physiological edema usually signifies a normal pregnancy, whereas pathological edema reflects protein, calorie, sodium, or related dietary deficiencies or a medical disorder unrelated to pregnancy. Since sodium restriction is indicated only in cases of heart failure and other rare diseases, attempts to limit sodium retention by advising a low sodium diet and administering diuretics actually stimulate the mechanism which promotes sodium retention [159,421].

The obstetrical theory that sodium should be restricted gave rise to an environment enabling the drug industry to promote diuretics as prophylaxis and treatment of toxemia. One large prospective study of diuretics, which claimed value in their use, is mentioned here as a statement of the history of the effort [175].

Reanalysis of this report confirms the work of others who had shown sodium depletion to be hazardous [14,175,421,448,584].

Three thousand and eighty-three unusually healthy pregnant women, none over seventeen years, participated in a study conducted by Finnerty and supported by the drug firm Merck, Sharp and Dohme. Those who had previous cardiovascular or renal disease, edema, hypertension, or albumin-

uria were excluded. None of the women began participating in the experiment before the twelfth week of pregnancy. Thiazide diuretics were prescribed to 1,541 pregnant women; the control group was the 1,542 women without the diuretic.

Finnerty defined toxemia as an increase of at least 10 per cent in mean arterial pressure and/or the presence of albuminuria not caused by infection. This is at variance with a number of well-known definitions of diagnostic criteria.

Hughes [250], writing in 1972 for the Committee on Terminology of the American College of Obstetricians and Gynecologists (ACOG), as cited and enhanced by Chesley (arguably the premier researcher on toxemia during the middle half of the 20th century) [98], proposed four criteria for diagnosis of gestational hypertension:

1. Sustained rise of ≥ 30 Torr (mm Hg) in systolic pressure,
2. Sustained rise of ≥ 15 Torr in diastolic pressure,
3. A sustained systolic pressure ≥ 140 Torr, and
4. A sustained diastolic pressure ≥ 90 Torr.

Sustained was defined as a value on at least two occasions at least 6 hours apart. Note Hughes' use of *gestational hypertension*, a forerunner of the current term, *pregnancy-induced hypertension* (PIH).

More recently, Emanuel A. Friedman summarized the criteria as part of a work on decision-making algorithms in obstetrics [186]. Friedman distinguished critical blood pressure values between those of PIH (p. 58) and chronic hypertension (p. 70). The criterion for diagnosis changed with the progress of pregnancy. The diagnostic threshold for midtrimester mean arterial pressure (MAP = diastolic + a third of the pulse pressure difference between systolic and diastolic values) was ≥ 90 Torr. The threshold in the third trimester, and blood pressure over 135/85 was to be considered abnormal. Friedman rejected the popular 140/90 rubric, in line with the recognition that normal volume expansion in pregnancy is accompanied by lower diastolic pressure readings until very late in the third trimester [98, p. 6]. Friedman noted that treatment of pregnant individuals with chronic hypertensive disease did not improve fetal outcome when maternal blood pressure was less than 170/110 [186, p. 70].

In Finnerty's drug study, 5 per cent of women on thiazides developed toxemia, whereas 15 per cent of controls were diagnosed as having toxemia. Excluding neonatal deaths, 5 per cent of the drug group, versus 12 per cent of controls, had low birth weight infants. Perinatal mortality was 0.7 per cent in the drug group versus 5 per cent for the controls. Thus, superficial analysis suggests that diuretics will reduce the incidence of toxemia, perinatal mortality, and low birth weight. A thorough review of the study and its design demonstrates, rather, the contrary.

The differences in these outcomes between the two groups were due not to use of diuretics, but to the fact that women in the drug group suffered less iatrogenic sodium depletion and were in much better prepregnancy health than the women in the control group. Moreover, the design of the study was markedly biased in favor of the drug group. Even Finnerty admitted that the drug group, because they were given more medical care and attention, were probably more conscious of their health and that of their children to be:

It is . . . reasonable to suppose that the specific attention given to the treated group persuaded them to take better care of themselves. . . . It is recognized that certain differences did exist between the treated and nontreated groups which may have influenced the fate of the fetus. [175]

Specifically, comparative health status of the two groups was polarized by the previous exclusion of women with bacteriuria from the drug group. Control patients with bacteriuria, 22 per cent of that group, were not excluded from the study. Hence, roughly 339 more patients in the control group had clinical evidence of bacteria in the urine, a marker for urinary tract infection with profound influences on the outcome of pregnancy. The virulence of conditions manifested by bacteriuria was pronounced. Among women in the control group, 46 with kidney infections had low birth weight infants and eight had stillborns.

Significantly, medical and clerical personnel who provided antenatal care and related services were aware of the group to which each women belonged. Two hundred and one women *who were known not to have taken* the diuretics prescribed to them were transferred from the drug group to the control group. Since at least 13 per cent of women specifically receiving more medical attention were noncompliant, it is doubtful that the experiment was properly administered. Finnerty noted:

It might be argued that since the public health nurse found 201 of the "treated" subjects not taking medication, more frequent visits or closer questioning might have revealed a large number.

The rates of low birth weight, perinatal mortality, and toxemia among these 201 women, essential to the significance of the interpretation of the study, were not provided.

As mentioned previously, the women taking diuretics did not suffer as much sodium depletion (which diuretics promote) as the women in the control group, a fact which Finnerty failed to indicate. Initially, no dietary restrictions were imposed upon women in either group. One immediate effect of the use of diuretics is an increase in the appetite for salt. Since women taking diuretics were allowed the freedom to salt their food to taste, they were inclined to increase their intake of salt. Hence, their chance of

experiencing electrolyte imbalance, a result of hyponatremia and hypovolemia from diuretics, was minimized. On the other hand, the 915 women in the control group who developed edema (excepting edema of the lower extremities), albuminuria not due to infection, or showed at least a 10 per cent increase in mean arterial pressure were placed on a "sodium-free diet" and were given 100 mg of hydralazine daily. This regimen, as discussed previously, may lead to hyponatremia and hypovolemia and potentially exhaust the adaptive mechanism [421]. In addition, since sodium-free diets are usually low in high quality proteins, it is possible many of these 915 women developed hypoalbuminemia. It is unfortunate that statistical analyses were not provided for this subgroup, since they probably accounted for much of the toxemia, low birth weight, and perinatal mortality.

Subsequent double blind diuretic studies have conclusively shown that diuretics are of no value in human pregnancy [177,297,556]. Diuretics, which may impair placental function [96] and fetal growth, may lead to neonatal thrombocytopenia [96], hypoglycemia [56], or electrolyte imbalance [56,96], and maternal complications, such as toxemia [46,56,480], or pancreatitis [59, 368,377]. Potent diuretics can cause maternal death [54,241,377].

These and other deleterious actions of thiazide diuretics were discussed thoroughly at a public hearing of the Obstetrics and Gynecology Advisory Committee of the Food and Drug Administration's Bureau of Drugs on July 17, 1975 [584]. Nutritional, physiological, teratological, toxicological, and clinical arguments against use of thiazides in pregnancy, either as "preventative" or for "treatment" of toxemia, were detailed by obstetricians, public health physicians, an obstetrical physiologist (Chesley), and an obstetrical and neonatal pathologist.

The transcript of the hearing, lasting over three hours, fills 98 pages. Representatives of the FDA working staff and of ACOG's Committee on Nutrition also spoke. Most noteworthy is the fact that no testimony was offered in defense of any use of thiazides or any other diuretics in pregnancy. Clinical judgement on use of these drugs in the extremely rare cases of chronic congestive cardiac failure or in decompensating nontoxemic renal disease was discussed and recommended by several of the speakers. Moreover, almost all speakers took the salutary position that evidence should be required on the efficacy and the physiological appropriateness of diuretics before permitting their use, not that evidence of harmfulness should be required in order to bring about their removal from the market for use in pregnancy.

Teratogenic effects have been described through electrolyte imbalance leading to renal malformations [116].

As I previously stated elsewhere:

Modern renal physiology makes it clear that the use of diuretics in pregnancy has little or no basis. In fact, they pose a significant risk of sodium depletion. The one role they might serve is in the case of heart failure, but these instances are, of course, rare. There is a strong body of belief that diuretics may be causative of complications. *The use of diuretics in pregnancy should be banned; they should be abandoned in modern prenatal care* (emphasis added). [487]

Low salt diets and diuretic therapy can lead to a decrease in uterine blood flow (due to hypovolemia) or placental perfusion [96,333], thereby limiting the fetal supply of nutrients. A recent study demonstrated how this therapy compromises placental perfusion [496].

The study showed that the use of a low salt diet and the administration of diuretics dramatically decrease the metabolic rate of the steroid dehydroisoandrosterone sulfate (DHAS), which reflects the placenta's synthesis and secretion of estrogens. In normal pregnancy, the placental clearance of DHAS, which is converted to estradiol by the placenta, rises rapidly as pregnancy advances [496]. Pregnant women with preeclampsia or pregnancy-induced hypertension have decreased placental clearance of DHAS, about 50 per cent, and volume distribution of DHAS is decreased 60 per cent in less than eight days following salt restriction and the use of diuretics. In addition, the glomerular filtration rate (GFR) declined 20 per cent and blood urea nitrogen (BUN) increased approximately 200 per cent. It is of significance that GFR, BUN, and the clearance rate and volume distribution of DHAS all began to approach their normal levels within a few days after discontinuing the low salt diet and diuretic treatment.

These data are evidence that placental synthesis of steroids is dependent upon uteroplacental blood flow, which is depressed by the use of low salt diets, diuretics, or both.

The hyponatremia of salt restriction and the administration of diuretics can, if prolonged, lead to vasomotor collapse and eclampsia [421]. The consequences of low salt diet and diuretic therapy are usually more severe than is suspected, since glomerular lesions appear before the onset of clinical signs of sodium depletion [209]. Even though the increased activity of the renin-angiotensin-aldosterone system can adjust to restore much of the water and sodium balance, marked sodium depletion may appear during the adjustment period. Besides hyponatremia, such therapy can result in reduced levels of sodium in muscle and bone in addition to hyperkalemia [420]. The hemoconcentration caused by sodium restriction increases the hematocrit [420], masking the anemia. This is the reverse side of the reason Kerr Grieve corrected his *gestational index* for transfusions.

When the synthesis of renin cannot keep pace with renin secretion, the granules do not accumulate [419]. Pregnant women on a low sodium diet

usually excrete substantially more products of aldosterone metabolism than gravid women following normal sodium diets [209]. Hypertrophy and hyperplasia of the adrenal zona glomerulosa usually accompany the increase in aldosterone secretion [420,421]. In the sodium depleted state, as sodium excretion decreases, the zona glomerulosa increases in width [419]. That the exhaustion of this system is caused by sodium depletion is further demonstrated by providing a sodium load, which alleviates the pathological process [420].

By injecting aldosterone in rats, Pike demonstrated that sodium restriction during pregnancy causes the retention of more sodium than it does during a period of salt and water equilibrium [420]. Among rats on a low sodium diet, giving aldosterone resulted in a significantly ($p<0.001$) decreased rate of sodium excretion, showing nearly all the sodium in the body would be reabsorbed if the rat were sodium depleted. Injections of aldosterone increased sodium reabsorption only among those rats who were on a moderately or severely restricted sodium intake. Rats on a normal or high sodium diet showed an increase in renin granules after administration of aldosterone. However, if sodium was restricted, there was no increase in renin granules, since the sodium deficiency stimulated additional renin synthesis which prevented degranulation of the juxtaglomerular cells. For rats on a low sodium diet, aldosterone did not reverse hyponatremia or hypovolemia, as the hematocrit and plasma sodium levels were not significantly altered [420].

Women who develop toxemia as a result of following low salt diets or taking diuretics usually have markedly low secretion of renin and aldosterone, reflecting exhaustion of the mechanism [421]. When preeclamptics are given a sodium load, a decrease in sodium excretion signifies they are sodium deficient, not that their ability to excrete sodium is impaired [366,473]. Bower demonstrated that preeclamptics on high salt intake (25 g daily) gave birth to larger infants compared to low salt intake (2 g) [51]. The perinatal mortality rate was lower for women on the high salt diet.

Even in a clinic where nutritional education was not a fundamental aspect of the prenatal care regimen, the incidence of toxemia was reduced merely by allowing pregnant women to salt food to taste and by forbidding the use of diuretics. Abandoning the use of low salt diets and diuretics reduced the incidence of preeclampsia to a single case in 5,300 deliveries (0.0188 per cent) [102]. In a nearby clinic, one where hazardous salt depletion regimens were used, the incidence of preeclampsia was almost a hundred times higher (1.085 per cent). The comparison comes from India where low standards of nutrition were common in the 1970s [196].

The study of 2,019 pregnant women by Robinson [448], noted above, also

demonstrated that salt restriction induces toxemia. For every age group and each parity, the incidence of toxemia was higher among women told to restrict their consumption of salt. Furthermore, women who developed toxemia experienced an alleviation or reversal of the disorder when given additional salt. In general, the greater the amount of salt the toxemic women added to their diet, the faster they recovered. In contrast, women who developed toxemia but did not increase their salt intake, often had an exacerbation of or, at best, no alleviation of the disorder.

PATHOGENESIS OF GESTOSIS

Preeclampsia/eclampsia, toxemia, and gestosis are various terms offered over time for the condition referred to as metabolic toxemia of late pregnancy by T. H. Brewer [53-61]. Since toxemia of pregnancy is frequently a precursor of developmental disabilities, a discussion of the causes, prevention, and treatment of toxemia is indicated. Of various maternal complications of pregnancy, gestosis is perhaps the most accurate indicator of fetal and newborn health. Toxemia was first described more than 2,000 years ago and there have been countless theories, most of them mythical speculations, propounded and unfortunately taught as gospel. Moreover, the many historic means of preventing and treating toxemia were just as irrational as the theories on etiology [53,54,56,60,96,241]. Chesley made this abundantly clear in his section on *Hypotheses* and rational management (pp. 26-30) and Chapter 17, *Hypotheses* (pp. 445-476 [98]).

Although its cause was discovered over sixty years ago [57,456,458,515,524], toxemia was still referred to as "the mysterious affliction" in 1972 [57], "the disease of theories," or "the ancient enigma of obstetrics" in 1973 [599]. Actually, toxemia seems to be "a disease of prejudice" [600]. Chesley, as noted above, considered by many to be the leading expert of his day on the pathogenesis of toxemia, stated:

Everyone from allergist to zoologist has proposed hypotheses (about toxemia) and suggested rational therapies based upon them, such as mastectomy, oophorectomy, renal decapsulation, trephination, alignment of the patient with the Earth's magnetic field with her head pointing to the North Pole, and all sorts of medical regimens. [599]

Chesley neither described nor discussed animal disorders resembling human gestational toxemia; this was provided by B. H. Douglas in 1971 [145].

Considering the excess of speculations and patently unfounded theories about the etiology of toxemia which history records, it seems incomprehen-

sible that Theobald had a thorough understanding of pathogenesis more than sixty years ago [524]. He learned from extensive clinical practice that, contrary to past and then prevailing beliefs, toxemia was mediated through hepatic dysfunction and that “the kidneys play no part *in the causation* of the toxemias.”

In a clinical analysis of 68 toxemic women, Theobald, in the 1930s, independently determined that “all the ailments and toxemias associated with pregnancy are caused by an absolute or relative insufficiency of some substance or substances in the diet.” He further stated, “I believe that the toxemic symptoms of pregnancy are precipitated by inadequate available supplies of iron, iodine, and calcium, and possibly of other inorganic substances” [524].

While a vast amount of research has been conducted purportedly to isolate a toxin, Theobald demonstrated in the 1930s that no such pregnancy toxin could exist. Consequently, he proposed (and many concur today) the term “toxemias of pregnancy” be abandoned for a more accurate clinical description of the disease entity. Whereas Theobald suggested that toxemia be referred to as “*encymonic atelositesis*,” Brewer preferred the more descriptive term, “metabolic toxemia of late pregnancy” [56,57]. Theobald’s rejection of the theory that toxemia could be caused by a toxin was primarily based on the fact that severe toxemia frequently resulted in widespread lesions in maternal organs but did not similarly affect the organs of stillborn infants born to eclamptic mothers [524]. Another observation which led Theobald to realize that no such toxin existed was that blood from eclamptic women could be injected intravenously into animals without consequence. He observed:

The toxemic manifestations of pregnancy are extremely varied and differ widely, so that no system of the body escapes. There is no analogy for the assumption that these widely differing manifestations could be caused by one toxin – a dozen would hardly suffice. [524]

Given the plethora of nomenclature at the end of the 20th century, it is just as well that Theobald’s specific suggestion for the name of the condition was ignored totally.

During the same period in which Theobald observed clinically that toxemia of pregnancy was caused by inadequate nutrition, Robert A. Ross of North Carolina published his observations of the relation between dietary deficiencies and the disorder [456]. During the 1930s, Ross discovered that the incidence of eclampsia was extremely high in the areas of North Carolina which also had high rates of beriberi, pellagra, and other clinical disorders caused by obvious dietary deficiencies. Ross quoted statistics which showed that at the time of his paper, *maternal mortality* in North Carolina was a tragic

0.57 per cent [456]. He declared:

We have been struck with the number of patients in eclampsia who are in a very poor state of nutrition . . . The type of patient who we see in eclamptic convulsions is the patient who subsists on a 2900 calorie diet consisting of fat meat (probably salt pork), field peas, rice, hominy, grits, cane syrup, brown gravy, lard, and cornmeal . . . which is deficient in Vitamins B₂, A, C, and D, iron, calcium, phosphorus, and complete proteins. [456,457]

The fact that toxemia has been used to describe a syndrome (the development of edema, hypertension, and proteinuria) rather than a disease entity [57] has spread confusion to many seeking means of prevention and treatment. Over the years, treatment of toxemia has consisted of venesection, bloodletting [143], low protein diets [143], placing the patient in a dark room,¹ and numerous hazardous or worthless regimens.

Since numerous physiological phenomena can cause the same symptoms that characterize gestosis, a differential diagnosis should be used to determine the specific cause(s) of the symptom or symptoms [56]. The appearance of at least two of the symptoms of hypertension, edema, and proteinuria do not necessarily warrant a diagnosis of toxemia [515]. The historic treatment of toxemia, which consisted of weight control, salt restriction, and the use of diuretics, may temporarily alleviate one or more symptoms but actually is a major cause of the disorder. Such wholly unscientific treatment, which is characteristically symptomatic, not preventive, has created thousands of preventable instances of maternal and infant morbidity and mortality [53,60].

Preeclamptics usually have decreased secretion of aldosterone, indicating exhaustion of the salt conserving system [421]. Another factor indicating near exhaustion of homeostasis is the depression of the expected level of plasma renin substrate and activity [97]. Toxemia is usually accompanied by an increased concentration of serum uric acid. The albuminuria which usually accompanies gestosis may be caused by kidney damage resulting from severe sodium deficiency [421]. The formation of renal glomerular endothelial lesions usually precedes the development of malnutrition induced proteinuria [56,421].

More cellular and pathophysiologic detail on gestosis is now coming to the fore including basic processes such as apoptosis [137], and the possible role of cytokines [300,301,551], the meaning of enzymatic changes [471], vascular lesions [491], and the role of changes in cell organelles in pathogenesis [492].

Since the evidence is strong that metabolic toxemia of late pregnancy is a

¹ I well remember the dark room of Prevost Ward, Duke Hospital, in Durham, in the mid-1950s; the dark room would, at least, reduce the risk of triggering a convulsion from bright lights in severe preeclampsia. This is still recommendable.

disease of malnutrition [56], means of prevention and treatment are clear, when the metabolic aspects are taken into account.

Hepatic dysfunction always precedes the clinical symptoms of metabolic toxemia of late pregnancy. Hypoalbuminemia, due to protein/calorie or related dietary deficiencies, and hypovolemia, the result of dietary or iatrogenic salt depletion, impair the hepatic capacity to synthesize sufficient albumin and maintain enzymatic detoxification, one of the principal functions of the liver [55,258]. The fact that severe preeclampsia or acute eclampsia results often in specific hepatic periportal lesions or infarction provides further evidence that malnutrition is a major factor in hepatic dysfunction [456-458,493].

Hypovolemia or hypoalbuminemia precede the onset of Brewer's metabolic toxemia of late pregnancy [44,56]. One study showed the dramatically high correlation between toxemia and hypovolemia [505]. In fact, in the absence of heart disease or rare renal diseases, hypovolemia always precedes metabolic toxemia of late pregnancy [56].

During their last twelve weeks of pregnancy, hypertensive women were tested for possible plasma volume depletion [505]. Women with lesser degrees of volume depletion had uneventful pregnancies and deliveries without clinical fetal distress. In addition, the degree of volume depletion was shown to be directly related to the severity of complications.

Table 5-7 reveals the relation between hypovolemia and the character of the hypertension observed clinically, as measured against the expected plasma volume for body weight [505].

The greatest degree of volume depletion was found in seven cases of fetal distress, which cut across the lines of Table 5-7. These seven, three with severe preeclampsia, two with chronic hypertension with superimposed preeclampsia, and two mild preeclamptics, in combination, had an average plasma volume 39 per cent below normal.

In toxemic women, hypoproteinemia is usually more pronounced than hypovolemia [44]. It has been known for over a century that a decreased

Table 5-7
RELATIVE DEGREE OF HYPOVOLEMIA
BY TYPE OF HYPERTENSION IN PREGNANCY [505]

<i>Hypertensive category</i>	<i>Number of women</i>	<i>Plasma volume as per cent of expected</i>
Transient	24	80.0
Chronic	10	77.2
Preeclampsia or chronic with superimposed preeclampsia	9	62.5

serum albumin predisposes to eclampsia [455,457].

As noted above, Strauss recognized in the early 1930s that toxemia is due to malnutrition, particularly protein deficiency [515]. He observed the serum albumin of toxemic women was very low. The average daily protein intake of 20 toxemic women was less than 50 g. Strauss noted that 18 of them "had eaten little meat or other protein foods, not only during pregnancy but often over a period of years."

Of the 15 toxemic women on the high protein diet, Strauss noted: "No fetal mortality occurred after the institution of this special diet . . . In no instance was there any return of toxemic symptoms."

After three weeks on the high protein diet, the blood pressure of *all* fifteen women declined. The average blood pressure decreased from 160/110 to 120/75. In contrast, only two of the five toxemic women on the low protein diet showed a reduction of blood pressure. After two weeks on the high protein diet, the fifteen women lost an average of 2.9 kg; the five women on the low protein diet *gained* an average of 1.0 kg. None of the women on poor diets lost more or gained less weight than any of the women on the good diet. Furthermore, none of the women on high protein diets had increases in severity of albuminuria, and in many cases this was eradicated. In contrast, 40 per cent of those on the low protein diet had exacerbations of albuminuria.

Numerous other studies have shown that a high protein diet can reverse toxemia once it has developed. In the 1930s, Dodge and Frost observed that, in general, toxemic women who did not adhere to their instructions to abstain from consuming meat and eggs showed alleviation of the symptoms of toxemia, whereas the disorder became progressively worse in women who followed their dietary advice [143]. Consequently, they began to recommend a high protein diet to women who became toxemic. As a result, while previously there were several cases of eclampsia every year in their clinic, eclampsia was eradicated for four years after they began recommending the high protein diet for toxemic women. They observed that toxemic women who were placed on a daily diet which consisted of six to eight eggs, one to two quarts of whole milk, meat, and legumes improved dramatically.

To test the hypothesis that toxemia is a disease of protein deficiency, they compared serum albumin of eight toxemic women with 12 normal pregnancies with a high protein diet and 42 nontoxemic women on a regular diet. Except for the patients on a high protein diet, the albumin levels of the pregnant women were much lower than those of nonpregnant controls indicating that the gestational diets were insufficient to satisfy the nutritional stress of pregnancy. The average albumin among the toxemic women was 21 per cent lower than those on the high protein diet.

Dodge and Frost demonstrated beyond a shadow of a doubt that the blood albumin of toxemic women is lower. In their study, the difference between the serum albumin among the toxemic women and those of nontoxemic women, whether on regular or high protein diets, is extraordinarily significant statistically (Table 5-8).

Table 5-8
SERUM ALBUMIN AND GLOBULIN IN TOXEMIA [143]

	<i>Number of women</i>	<i>Serum albumin</i>	<i>Serum globulin</i>
Toxemic	8	3.87 ± 0.03 g/dl	2.07 ± 0.09 g/dl
Nontoxemic regular diet	42	4.04 ± 0.04	2.25 ± 0.05
Nontoxemic high protein	12	4.90 ± 0.09	1.76 ± 0.12
Nonpregnant	34	4.90 ± 0.06	1.88 ± 0.06

Values are means ± standard error (S.E.M.)

The probability that the difference was achieved through chance, i.e., there was no relationship between low serum albumin and toxemia, is much less than one in a million [143].

Mitchell et al. confirmed the findings of Dodge and Frost that toxemia is basically a disorder caused by protein deficiency [378]. During the late 1940s, they studied the dietary intakes of 33 severe preeclamptics, all residing in a rural three-county region in Alabama, and compared diets of 59 nontoxemic controls from similar socioeconomic backgrounds in the geographical area. When provided a diet with an average of 124 g of protein daily, the severe preeclamptics exhibited marked improvement.

In comparing the diets of the preeclamptics with those of the controls, the authors stated:

The control group had an average protein intake of 75 grams daily. The severe preeclamptics had an average protein intake of 40 grams daily. A great portion of the protein intake of the preeclamptics was not superior protein, i.e., not animal protein of meat, fish, eggs, or milk. . . . It is significant that no case of preeclampsia was observed in any women receiving over 60 grams of protein daily. . . . To prevent hypoproteinemia, the diet must provide an abundance of good proteins. [378]

Tompkins and Wiehl markedly lowered the incidence of toxemia by supplementing the diets of pregnant women (Table 5-9) [534]. As previously stated, the protein supplement consisted of 50 g high quality protein and 1.5 g of calcium. The incidence of toxemia was much lower in women receiving both protein and vitamin supplements. The authors

Table 5-9
PREVALENCE OF TOXEMIA IN SINGLETON BIRTHS
BY TYPE AND DEGREE OF SUPPLEMENTATION [534]

	Number of Patients	Toxemia	
		Number	Per cent
Control	170	7	4.12
Added vitamins	244	8	3.28
Added protein	186	5	2.69
Added vitamins and protein	160	1	0.63

concluded: "The so-called 'toxemias of pregnancy' are in reality nutritional deficiency states."

The fact that protein deficiency causes toxemia was verified in a more recent study in which the provision of protein immediately alleviated the toxemic process [582]. Howard compared 297 women who were given phenobarbital and confined to bed rest after they developed toxemia with 135 toxemic women who received at least 25 g of albumin and "a liberal intake of salt." Creatinine clearance, which measures glomerular filtration, increased in every woman given human serum albumin intravenously. Urinary estriol also increased markedly in the albumin groups, demonstrating an improvement in placental function. Of the 37 cases of severe toxemia among the 135 given albumin, there was not one instance of infant respiratory distress syndrome (RDS), which frequently is associated with infant morbidity and mortality [42,43].

Table 5-10
PROTECTIVE EFFECTS OF SERUM ALBUMIN IN TOXEMIA [582]

	Number	Induced labor	Perinatal mortality	Placental abruption
Study group	135	5.0%	0.9%	0.0%
Control group	297	24.9%	3.7%	3.0%

Most important, all of the infants born to the 37 severely toxemic women receiving albumin were accorded fairly high pediatric ratings. All toxemic women receiving 50 g of albumin daily delivered infants in excellent health. The toxemic women who received albumin and adequate salt also had a dramatically lower rate of labor induction than women in the control group ($p < 10^{-5}$). None of the women in the former group had premature separation of the placenta (Table 5-10).

LOW UMBILICAL CORD PROTEIN AND RESPIRATORY DISTRESS SYNDROME

An exacting study of umbilical cord protein level and neonatal respiratory distress identified a pathogenetic relationship between protein levels and pulmonary disease [42]. Iyenger's protein study found higher serum proteins in cord blood, especially albumin ($p<0.01$) [257]. Low cord protein levels are usually associated with prematurity and neonatal distress, especially respiratory distress syndrome (RDS) [42,440], also known as hyaline membrane disease [484].

By study of umbilical cord blood protein of 2,200 consecutive births, Bland conclusively showed RDS with high neonatal mortality rate to be related to low cord protein levels [42,43]. Of great significance is only one of the 34 infants with RDS (2.9%) had a cord blood total protein concentration of greater than 4.6 g/dl. Nineteen of the 34 infants with RDS died (55.9%).

In contrast to the high incidence of RDS among infants with a cord protein of 4.6 g/dl or less ($33/98 = 33.67\%$), only 1 of the 2,102 infants whose cord protein was above 4.6 g/dl developed the disease (0.047%). The mean cord protein for all 2,200 infants was 5.89 g/dl. Among the 34 infants developing RDS, mean protein was 3.80 g/dl; the level of the 2,166 infants without RDS was 5.91 g/dl. This difference would occur by chance in less than one of a billion occasions. Of the infants with RDS, the cord protein was significantly lower among 19 deaths than for the 15 survivors ($p<0.01$) (Table 5-11).

Table 5-11
RISK OF RESPIRATORY DISTRESS SYNDROME, MORTALITY,
CORD PROTEIN LEVEL, AND LENGTH OF GESTATION [42]

	<i>Number of infants</i>	<i>Per cent RDS</i>	<i>Level of significance</i>	<i>Per cent mortality</i>
Low birth weight	171	17.54	10^{-12}	11.11
Weight >2500 g	2039	0.196		n.a.
Cord protein \leq 4.6 g/dl	98	33.67	10^{-12}	20.41
Cord protein >4.6 g/dl	2102	0.05		n.a.
Low birth weight and protein \leq 4.6 g/dl	60	50.00	10^{-15}	30.00
Normal birth weight and protein >4.6 g/dl	2140	0.19		n.a.
Gestation <37 weeks and protein \leq 4.6 g/dl	58	51.72	10^{-15}	32.76
Term pregnancy and normal protein	2142	0.19		n.a.

As would be expected from these findings, cord protein was also highly related to birth weight, length of gestation, and third trimester hemorrhage, all markedly affected by maternal nutrition. As both birth weight and length of gestation increased, cord protein rose. Among infants of 28 to 32 weeks

gestation who weighed between 1,000 and 1,500 g at birth, the average cord protein level was 3.8 g/dl; among normal weight infants at 40 weeks gestation, the mean protein level was over 6.0 g/dl. Since increased gestational age was found to be associated with a rise in colloid osmotic pressure, Bland inferred that "the plasma proteins of immature infants may be not only quantitatively deficient but functionally ineffective as well."

Of the 2,176 infants without antepartum hemorrhage, the mean cord protein level was 5.91 g/dl; the protein among 24 infants of mothers with late pregnancy hemorrhage was 4.90 g/dl ($p < 10^{-7}$). Table 5-11 and Figures 5-5 and 5-6 demonstrate the dependent relationship between cord protein, birth weight, and length of gestation and their independent effects in the risk of RDS and infant mortality. Of the infants with RDS, the average birth weight was 1,570 g; the mean length of gestation was 31 weeks. It is noteworthy that among the 34 study infants with RDS and 72 subsequent cases of RDS from the same hospital (only one of these infants had a protein level over 4.8 g/dl),

Probability of RDS

BIRTH WEIGHT
IN GRAMS

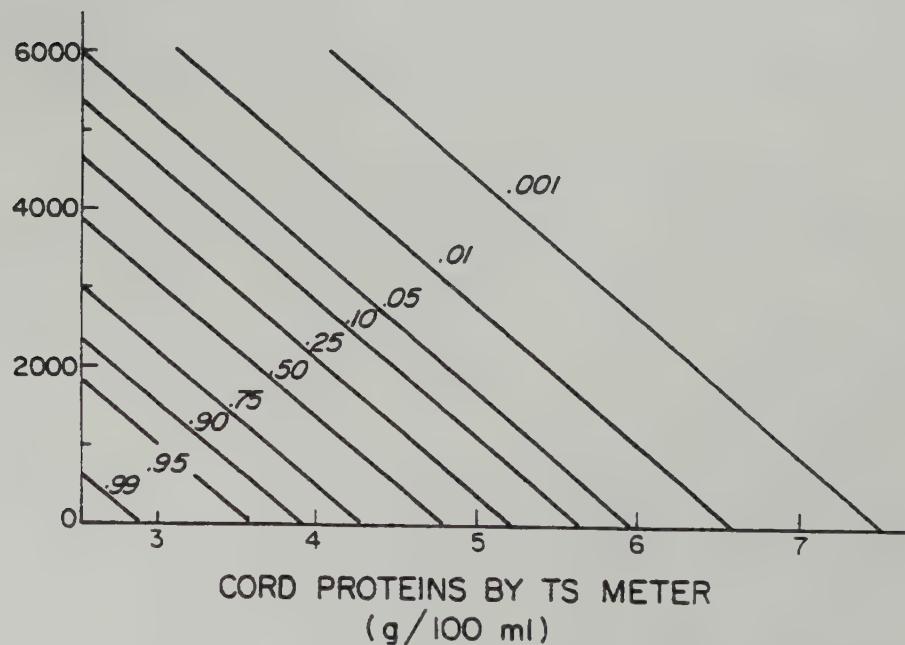


Figure 5-5. Nomogram for determining risk for respiratory distress syndrome (RDS) of prematurity by birth weight and cord protein level. (Courtesy of Richard D. Bland, M.D.)

Probability of RDS

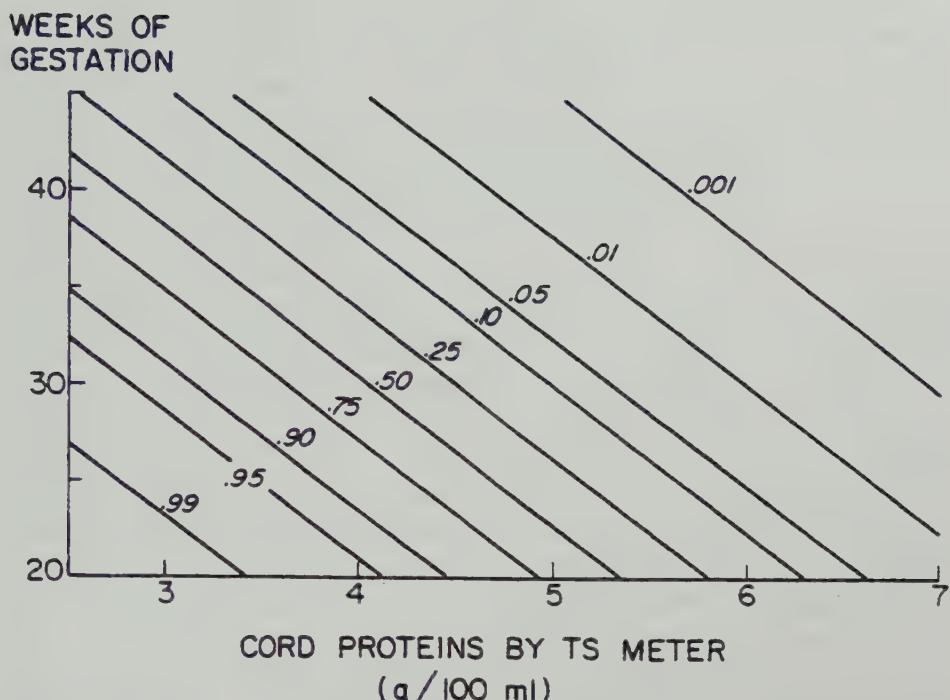


Figure 5-6. Nomogram for determining risk for respiratory distress syndrome (RDS) of prematurity by gestational age and cord protein level. (Courtesy of Richard D. Bland, M.D.)

not one infant death occurred in when cord protein was greater than 4.6 g/dl.

An independent study of 1,000 births showed the incidence of RDS among infants with cord protein over 4.7 g/dl was 3.9 per cent, whereas the incidence of RDS in infants with less cord protein was 21 per cent [440]. In addition, among infants with RDS, as cord protein levels decreased, the severity of RDS increased.

The important results from these studies of RDS, coupled with Iyenger's finding of the causal relationship between inadequate maternal nutrition and low cord protein levels, have overwhelming implications for the prevention of RDS and the resultant morbidity and mortality. These are remarkable results, especially in light of the complex metabolism of albumin [463].

In 1972, more than 25,000 infants in the United States died from RDS [583], many more than the 1,815 specifically attributed to RDS and the 4,310 attributed to preterm delivery and low birth weight, recorded by C.D.C. in

1993 [616]. The difference, which is both significant and praiseworthy, is due largely to availability of and the skills found in neonatal intensive care units across the United States. The necessity for such units and services will be decreased only by full implementation of the means for prevention which these many studies urge compellingly.

CARBOHYDRATE INTOLERANCE, HYPERINSULINISM, AND GESTOSIS

An association between hyperinsulinism and gestosis was observed more than six decades ago by Titus [531]. Hypoglycemia, which can result from a deficiency of high quality proteins or other essential nutrients, is a frequent characteristic of preeclampsia. Eclamptics often experience a precipitate decrease in blood sugar. If convulsions occur, the blood sugar usually fluctuates considerably during the seizures.

Apparently unaware of the much earlier report of Titus, Long et al. [337] more recently described in detail the relation of toxemia to pancreatic islet function. They studied 794 women with preeclamptic singleton pregnancies by 3-hour glucosetolerance tests given between 32 and 34 weeks of gestation. Of the preeclamptic/proteinuric women, 22.3 per cent were hypoglycemic, 1.5 times the general rate for that hospital population which was 14.8 per cent ($p<0.05$), a significant difference. Low estriol levels were found in 26.5 per cent of the women with both preeclampsia and hypoglycemia, a frequency significantly higher than that for normoglycemic preeclamptics. Birth weights in the 10th or lower percentiles occurred in 18.8 per cent of such infants. Moreover, a high perinatal mortality was observed when both hypoglycemia and preeclampsia were present: 40/1000 live births.

Interestingly, Long et al. also found a four-fold increase in *hyperglycemia*, defined as blood glucose above the 95th percentile of their general hospital experience. This frequency, 21.4 per cent, was significantly different ($p<0.01$) [337].

EVIDENCE FROM THE DIABETIC STATE

Metabolic aspects of fetal and neonatal growth were reviewed in 1992 by Battaglia [31]. For a variety of reasons, the review concentrated on glycine, leucine, and glucose. Glycine and leucine were considered as representatives of amino acid metabolism. There is little uptake of glycine from the *fetal* circulation and no glycine oxidation was found to occur in the placenta. The

fetal liver accounted for 70 per cent of total fetal glycine oxidation.

Battaglia noted that circulating fetal amino acids may not be from the mother by diffusion or facilitated transport at all but were resynthesized in the placenta. The placenta delivers a supply of amino acids to the fetus in both mid and late gestation which exceeds the requirements for net protein accretion [88]. Leucine, an essential amino acid, shows a high fetal rate of oxidation, up to 25 per cent, but not in the placenta. Leucine is not simply transported (viz, some is, some is not); rather, its deamination product, α -keto-isocaproic acid, is delivered into both the umbilical and uterine circulations [280,341,544].

In midgestation, fetoplacental transport of glucose rises due to the onset of capacity to regulate the process. This is partially due to the mass growth of placenta but an upregulation of glucose transporter molecules or cofactors is very likely part of the equation as well. A relationship of cord blood peptides to maternal insulin sensitivity and birth weight had been observed [36].

Battaglia's insight is almost certainly correct. "Protein" is transported across the placenta by specific amino acid transporter proteins [162,236]. Experimentally, these are regulated, at least in part, by protein intake [200].

Transplacental alanine transport follows this pattern. Placental uptake of alanine from maternal blood is exchanged for placental alanine which is secreted into the fetal system [529].

Godfrey et al. studied the uptake of neutral amino acids by the microvillous plasma membrane of the human placenta. They found neutral amino acid uptake is inversely related to fetal size at birth in normal pregnancy. Although fetal growth directly reflects net placental transfer, the cellular interactions are largely unknown. Analysis of methylaminoisobutyric acid uptake by vesicles allowed estimates of: (1) system A neutral amino acid transporter activity, and (2) diffuse permeability. Smaller infants with lower abdominal circumferences had higher placental system A activity per mg of membrane protein ($p=0.004$); activity rose from 0.020 to 0.043 nmol/30 sec/mg protein as abdominal circumference fell from 34.6 cm or more to 32.0 cm or less. Infants with smaller abdominal circumferences also had higher sodium independent amino acid uptakes ($p=0.0005$); compositional changes in trophoblast plasma membrane seem to be the most likely basis for these responses but the ultrastructural aspects have not been described.

Two systems have been identified so far, one noted above, the system A amino acid transporter, and two, the system L transporter. Kuruvilla et al. examined both systems in concert with the Na^+/H^+ exchanger in placentas from pregnancies resulting in macrosomic infants [302]. There were two comparison groups: (a) fully normal pregnancies, and (b) appropriate fetal growth for gestational age in diabetic women. Sodium-dependent uptake of

[¹⁴C]-methylaminoisobutyric acid at 30 seconds (initial rate, a measure of system A activity, as noted by Godfrey et al. [200]) was reduced only in macrosomic placentas, to 49 per cent. Neither system L or the Na⁺/H⁺ exchanger showed similar or other changes. It was determined that the specific activity was normal with the effect due to a reduction in the number of transporter protein molecules or sites per milligram of membrane protein. The functional result is thus highly selective.

Distinctive patterns of amino acids occur quite early in human pregnancy [264,265]. Trophoblast provides nutrient transport and protein synthesis, resulting in high concentrations of amino acids in the placenta and fetal blood during the second half of pregnancy. Jauniaux et al. studied free amino acid distribution inside the first trimester human gestational sac. The data indicated the process began as early as seven weeks [264]. Taurine, glutamic acid, glycine, and alanine showed the highest concentrations in placenta.

Animal experiments confirm the essence of these processes. Wu et al. found maternal dietary protein deficiency decreased the amino acid concentration in fetal plasma and the allantoic fluid of pigs [572].

Two genetic lines were studied, one with low and the other with high plasma cholesterol. Dietary protein restriction in the two models led to decreases in: (1) maternal plasma concentrations of urea at 40 and 60 days; (2) fetal plasma alanine, arginine, branched chain amino acids (BCAA), glutamine, glycine, lysine, ornithine, proline, serine, taurine, threonine, and tyrosine at 40 days; (3) amniotic and allantoic fluid levels of urea at 40 and 60 days, and (4) allantoic fluid levels of alanine, arginine, BCAA, citrulline, cystine, glycine, histidine, methionine, proline, serine, taurine, threonine, and tyrosine at day 40 in both lines.

Studies on the placenta of the rat revealed low protein diet induced intrauterine growth retardation which was accompanied by downregulation of specific amino acid transport proteins [352].

Changes in placental protein content [431,432] and amino acids are seen in human material [90,385], including late pregnancy material. Gestotic placentas had less protein and lower DNA/protein ratios [433,434]. Morris et al. found growth retarded third trimester villi had significantly higher levels of two essential amino acids: phenylalanine and L-arginine. Nonessential amino acids with higher levels in growth retarded villi were: glutamic acid (versus normotensive normals) and tyrosine (versus gestotics). No change in the glycine/valine ratio, a marker for kwashiorkor, was found [385].

Interestingly, Cetin et al. found normal pregnant women to have lower levels for most amino acids in the second and third trimesters. Growth restricted pregnancies, by contrast, had significant elevation of most essential

amino acids compared to normals. Fetal levels of essential amino acids were decreased, making for large maternofetal differences [90]. This seems to be a paradox: the mother piles up amino acids and the fetus becomes growth retarded, with lower levels of amino acids. One might conclude that something, or some substance, was blocking the normal placental resynthesis of amino acids and peptides.

Comparative analysis of metabolic changes during pregnancy in diabetic and nondiabetic subjects has produced interesting findings [439]. Insulin secretion increases throughout normal pregnancy, but peripheral insulin sensitivity decreases. Insulin infusion to specified levels in pregnant sheep reduces peripheral glucose utilization [235]. An interaction between placental lactogen, progesterone, and triglycerides [320] promotes post-receptor decrease in insulin action in rat adipocytes [537] which is most prominent in skeletal muscle [79,538].

Fasting plasma glucose in the human falls about 10 per cent in the first trimester and maternal amino acid levels decline during pregnancy. Both cholesterol and triglycerides rise in the second trimester. Progressive amounts of contrainsulin hormones are secreted as pregnancy goes on and in 2-3 per cent of human pregnancies, this leads to gestational diabetes. In overt insulin-dependent diabetes mellitus, the insulin-deficient state results in fasting and postprandial hyperaminoacidemia, hyperlipidemia, and hyperglycemia [439]. This is seen also in hypoglycemic small for gestational age infants [370]. These changes lead to a hypermetabolic milieu which promotes fetal macrosomia and placental gigantism [167]. The sequential linkage of these anatomical attributes is not clear, but it is possible the latter occurs before the former. It is a question of disturbed calorie homeostasis [234]. The rise in free fatty acids due to secretion of human placental lactogen (HPL) serves as a maternal energy source, seemingly freeing up amino acids and glucose for the fetus [274,470]. The effectiveness of this would depend on the efficiency of placental resynthesis of amino acids. Fetal amino acid levels are three to four times maternal, but placental levels are higher still [106,439].

Insulin is a growth factor for the fetus. Hyperglycemic carbohydrate surplus leads to increased insulin secretion and fetal hyperinsulinemia. Fetal macrosomia does not require maternal hyperglycemia [367] since euglycemic diabetic women also produce macrosomic children. The basis for this seeming paradox is partially resolved by the finding that labelled maternal and fetal contrainsulin antibodies are strongly correlated, indicating transplacental passage of an antibody:insulin complex, which adds to the active insulin pool in the fetus.

Transient hepatic immaturity, in the form of delayed development of rate-limiting gluconeogenic enzymes, has been implicated in small for gestational

age infants [237]. Experimentally, gestational peripheral insulin resistance, which can be quantified [127], does not occur in the liver [120].

Moderately sophisticated methods of neonatal anthropometry have shown correlation between types of growth impairment and the risk of neonatal hypoglycemia [369]. This points to the prospect that a better understanding of the growth potential of the fetus in the maternal diabetic state should come from application of the same parameters. Mestyán and Járai designed an assessment grid which is slightly modified in Table 5-12.

Table 5-12
CLINICAL APPLICATION OF INDICES OF
ASSESSMENT OF NUTRITIONAL STATUS [369]

<i>Basic definitions:</i>		
Index or item	Useful for	Not useful for
Weight for age [as a single datum]	Rough index of nutritional status, uterine growth	Does not distinguish between: undersize and undernourished, OR overnourished and oversized
<i>With clinical assessment:</i>		
Combined weight and length deviations by age		
Four nutritional categories: A. Mildly retarded (in both) Weight deficit <30% Length deficit <15% C. Mildly by weight, severe by length Weight deficit <30% Length deficit >15% D. Severe by weight, mild by length Weight deficit >30% Length deficit <15% B. Severely retarded (in both) Weight deficit >30% Length deficit >15%		

n.b. Original categories have been reordered for more logical sequencing.

Expansion of body weight (mass) and length measurements were proposed as a means to provide better risk assessment. The paper attempted further correlation with nutritional indexes. Early neonatal hypoglycemia correlates well with this scheme. The percentile of body mass against glucose level has a definite pattern (Table 5-13). Two dimensional plots reveal a near linear relationship; the higher the percentile rank the higher the glucose level (data not shown). This illustrates a principle but neither the differences nor the trend are prognostic by case.

Table 5-13

INCIDENCE OF HYPOGLYCEMIA IN FIRST TWELVE HOURS AFTER BIRTH [369]

Weight deficit per age	Length deficit per age		Total
	<15% Mild	>15% Severe	
<30% Mild	15/115 A = (13.0%)	0/3 C = (0.0%)	15/118 (12.7%)
>30% Severe	23/62 D = (37.1%)	4/53 B = (7.5%)	27/115 (23.5%)
Total	38/177 (21.5%)	4/56 (7.1%)	42/233 (18.0%)

Declines in glucose levels postnatally are greater for infants less than the 15th percentile length deficit compared to infants above this threshold (Table 5-13).

This is an interesting pattern. Severe weight deficit plus mild length deficit probably means a more recent deprivation with particular impact on glycogen stores (liver and skeletal and cardiac muscle). Severe deficits in both groups is a form of *compensated* effect in that short body length minimizes the influence of weight loss or restrained weight gain. Comparison of groups B and A suggests that weight deficits have twice the effect of length changes, when taken as singular events. Mestyán and Járai plotted the ponderal index and weight for length factor against frequency of hypoglycemia (not shown). Prevalence of neonatal hypoglycemia progressively fell as both factors increased, an inverse linear relation to frequency of hypoglycemia, starting at 50 per cent at PI = 1.5 and falling to near zero at PI = 2.7. The plot against weight/length ratio was less precise below -15 per cent, their cutoff threshold in the calculations. Of special interest was the further observation that immediate postnatal blood glucose was not related to the ponderal index; rather, this has a more or less constant level (likely due to intrapartum events). Blood glucose values at 12, 24, and 48 hours post natal were all strongly correlated with the ponderal index: glucose: $r = 0.27, 0.27$, and 0.28 respectively.

On the other side of the birth transit, changes in maternal glucose levels have an acute effect on the fetus [373]. Muscular activity increases significantly for the first 30 minutes after maternal ingestion of 100 grams glucose and does so particularly during the last ten minutes of this interval (post threshold effect). The authors stated, erroneously: "... no correlation could be found between absolute levels of glucose at any measured level and fetal activity." However, a superimposition plot of the various movements and

fetal heart rate shows a remote and damped similarity between blood glucose and heart rate and, quite remarkably, a near overlap between blood glucose and simple movements. Simple movements were as defined by Timor-Tritsch et al. [530].

A similar but more detailed study was performed by Aladjem et al. [8]. Measurements of fetal activity were taken the morning after overnight fasting and after maternal glucose loading, 100 gm by mouth or 0.5 gm/kg intravenously. The fetal activity involved both fetal heart rate and physical movement. These were found to correlate with perinatal morbidity and mortality. There were 39 control and 54 study patients. Fetal movements (FM) were: (1) isolated, 12 seconds or more apart, and (2) multiple, a series of isolated movements <12 seconds apart from each other, with an average of four per group. Despite the relatively small sample, if the multiple: isolated increase was greater than 100 per cent (which occurred in 91.4 per cent of cases), the newborns were normal 98.82 per cent of the time, 84 out of 85; only 1/85 was abnormal (1.18%). If the increase was less than 100 per cent, the reverse was true: 7/8 abnormal, 87.5 per cent and 1/8 normal, 12.5 per cent. There was a similar damped relationship between FHR response and glucose level.

The outcome of pregnancy complicated by diabetes was studied thoroughly by Plehwe et al. in 232 patients over a four-year period [423]. The study was divided into two groups. Group one consisted of 72 insulin dependent diabetics; group two was mixed, with nine noninsulin dependent and 151 gestational diabetics. Overall perinatal mortality was 5.6 per cent. There was a high rate of malformations, 5.6 per cent major and 7.7 per cent minor (total = 13.3%). No differences in mortality or malformations were adduced between the groups. There was a reduced prevalence and severity of respiratory distress syndrome when pregnancy went beyond 37 weeks. They confirmed that maternal hyperglycemia in the third trimester is related to and likely a causal factor in neonatal hypoglycemia.

Maternal intravenous glucose administration has been confirmed as a cause of neonatal hypoglycemia [328].

Closely related to the problems of gestational and overt diabetic effects on fetal growth is fetal growth retardation in the underweight mother [462].

The fetal outcome of gestational diabetes is not always macrosomia. Fee and Weil demonstrated there is a small for gestational age outcome as well [167]. Their observations were purely descriptive. It remains to be seen whether the physical and chemical parameters are related to an exaggeration of the process of accelerated starvation [372].

A drop in food intake during pregnancy has more metabolic effect than in the nonpregnant state. Freinkel coined the phrase "accelerated starvation" to

describe this situation [184]. The key signal is a progressive fall in blood glucose which leads to active fat mobilization and increased gluconeogenesis [171,280].

Enhanced gluconeogenesis leads to proteolysis with marked and rapid changes in the amino acid profile [317,385]. Alanine, glutamate, and serine levels decrease while taurine, lysine, and 3-methyl-histidine increase. Catecholamine release, glucagon secretion, and the attendant hemodynamic changes also occur. There is increased blood flow to the liver and brain and less to the uterus [28,453,454]. After five to seven days of fasting, the uterine uptake of oxygen, glucose, and essential amino acids decreases nearly 50 per cent [317,385]. The fetus becomes hypoglycemic and fetal insulin release falls [30]. This leads to fetal gluconeogenesis, an 80 per cent increase in urea production, and major changes in plasma amino acid concentration. Most amino acid levels rise, including 3-methylhistidine (fetal proteolysis) [317]. This promotes a drop in the fetal oxygen:glucose quotient from 0.70-0.80 in the normally fed state down to 0.30-0.40 after five days fasting [317,385]. A quotient of 1.0 would indicate that only glucose is utilized for fuel. The growth and remodeling of fetal tissue might well account for some proteolysis normally, thus a background quotient of 0.70-0.80. It is not at all surprising that fasting fetal growth is severely compromised (196,313,363).

Total peripheral vascular resistance (TPVR) is higher in underweight mothers (albeit still in a normal range) [461]. In early pregnancy, TPVR falls as a result of rises in vasodilator hormones, and the low resistance circuit in the placental vascular bed [339]. A gradual adaptation to this would entail an increased plasma volume [339]. Failure to so adapt would mean, later in gestation, less plasma volume. Normotensive pregnant women have TPVR near term which are correlated with fetal weight [461]. Gestotic women have TPVR values which correlate roughly with uteroplacental blood perfusion [304]. No change has been found in plasma renin, but aldosterone is markedly reduced in the underweight gravida and sterol levels are decreased but this is significant only for estradiol. The rate of protein turnover, measured by leucine kinetics, is increased in insulin treated gestational diabetes mellitus [272]. Protein turnover can be normalized in insulin treated women with gestational diabetes mellitus. However, fasting and postprandial plasma amino acids were elevated in the antepartum and postpartum periods, despite effective maternal glycemic control [82].

In addition to its role as a (perhaps the) driving force in fetal growth, insulin-like growth factor-1 (IGF-1) (Figure 5-7) has marked antiproteolytic endocrine effects in the late gestational mammalian fetus [327].

Finally, the blood volume of infants of diabetic mothers (IDM) is greater than for normals and the residual placental blood volume for IDM after

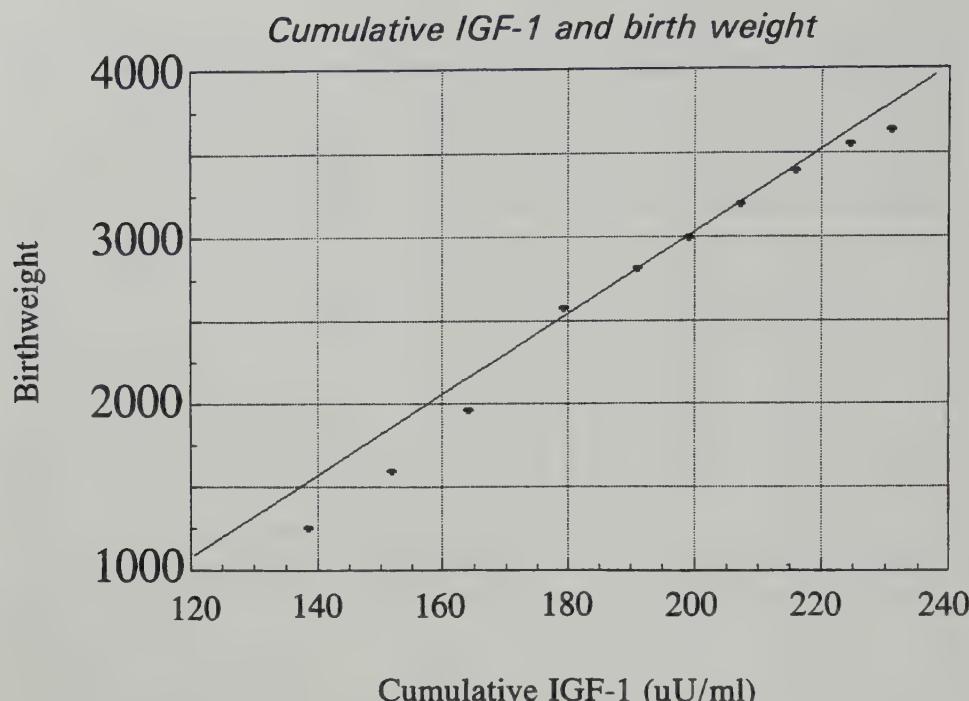


Figure 5-7. Relation of cumulative IGF-1 to birth weight. This shows high correlation whereas interval cross-sectional results do not. Since growth of the fetus is also cumulative, this method of estimation seems appropriate, *a priori*.

delivery is three times normal absolute (103.6 ml vs. 33.6 ml); the relative values are also high (Table 5-14) [287]. It is interesting that IDM have delayed onset of respiration. An early onset facilitates placental transfusion to the newborn. This may be related to ductal flooding of the pulmonary bed, encouraged by microvascular effects of surfactant.

Table 5-14
ABSOLUTE AND RELATIVE RESIDUAL PLACENTAL BLOOD VOLUMES [287]

	Mean total	Per 100 g placenta	Per kg birth weight
Infants of diabetic mothers	103.6 ml	14.9	28.4
Low birth weight	27.2	6.7	13.9
Nondiabetic term infants	33.6	5.5	9.3

A relationship between gestational diabetes and the subsequent onset of maturity onset diabetes mellitus has long been known [406]. Practical diag-

nostic criteria for diabetes in the puerperium were refined recently [110].

The possibility that impaired glucose tolerance in late life could be related to a fetal growth pattern was explored in an unusual case by Hales et al. [221].

Certain current social practices, such as the abuse of cocaine, may present as diabetic ketoacidosis [553].

THE AUSTRALIAN PROTOCOL

Hamlin, the medical superintendent of The Women's Hospital, Sydney, Australia, was perhaps the first physician to establish a rigorous program for the sole purpose of reducing the incidence of toxemia. Observing the rate of preeclampsia/eclampsia at hospital had not declined for more than a decade, Hamlin developed an effective program of applied scientific nutrition to eradicate eclampsia and reduce the incidence of preeclampsia in 1948 [223]. Consumption of meat, milk, eggs, and fresh vegetables was encouraged actively.

From 1936 to 1947, there had been 102 patients with eclampsia in 36,700 deliveries (0.278 per cent) [223]. Two years after Hamlin instituted the nutritional education program, there were no cases of eclampsia in 5,000 deliveries. Assuming the only difference in the prenatal care regimens between the 1936 to 1947 period and that of 1949 to 1950 was the increased emphasis on nutrition, the chance that the nutritional education program did not reduce the rate of eclampsia is less than 1 in 10,000 ($p < 0.0001$). In addition, Hamlin reduced the incidence of preeclampsia to 1.8 per cent. If weight gain had not been controlled and salt not restricted for edematous women, this success in lowering the incidence of toxemia would have been even more pronounced. Properly, however, Hamlin declared:

The damage (eclampsia), I believe, occurs at this stage when there is an imbalance of diet – an excess of carbohydrates and a relative deficit of first class protein and of vitamins . . . The attack (against eclampsia) succeeded because it was aimed strategically at the occult basis of the disease instead of at its summit of classical late signs and symptoms. [223]

Hamlin concluded eclampsia was probably of metabolic origin, a concept which was later verified and strongly promoted by Brewer [56]. He noted the rate of eclampsia in Australia was highest during late winter and early spring, attributing this high rate to inadequate diets during the summer and autumn months, when the local diets are relatively low in protein and high in carbohydrates [223]. The protein requirements during the autumn months for women who delivered during the winter months were exceptionally high. Hamlin noted also:

The humidcribs were often empty now. By 1949 nurses and medical students

were beginning to ask why they were no longer seeing enough eclamptics . . . By 1950 it was felt that one could say to the sceptics: "Eclampsia will no longer afflict the patients of this hospital if the present methods of prevention are followed meticulously" . . . The old conception that grave preeclampsia, with all its attendant problems and techniques of practical obstetric management, must always be with us has been disproved. [223]

A decade later, Hamlin reported from Ethiopia, declaring:

The astonishing low natural incidence of preeclampsia is the most fascinating thing about obstetrics in this country. Even among mothers who have had no antenatal care whatever, toxemia is rare. [224]

He was overwhelmed among cases he observed: the incidence of preeclampsia for unsupervised women in Ethiopia was 58 per cent lower (0.75%) than among women who attended nutritional education classes in Sydney. He attributed the low rate of toxemia in Ethiopia to consumption of teff, their chief cereal, which is rich in high quality proteins. Although the typical diet was low in calories and certain vitamins, it contained abundant protein, calcium, iron, and vitamin B₁.

Balfour showed that dietary supplementation during pregnancy markedly reduces the incidence of perinatal deaths caused by toxemia [22]. Her prospective study of the benefits of 21 months of food supplements documents the protective effects of maternal nutrition. The women who received the supplement, which consisted of milk, yeast, and vitamins and minerals, were selected from "the poorest [economic] classes." A control group was formed of women who attended the same antenatal clinics as the women in the study group but were not provided nutrition supplements, except for an unspecified quantity of milk, because of financial limitations. The combined incidence of stillbirths and neonatal deaths due to toxemia was 0.38 percent in the supplemented 11,618 pregnancies, in contrast to 0.56 percent in the control group of 8,095 pregnancies. This difference has borderline significance with $p = 0.0513$. This result, which intuitively might seem to have been more significant, due to the relatively large numbers of pregnancies in each group, actually points forcefully to the problem when the possibilities for change are small in any case. Perinatal death rates of the order of 0.38 to 0.56 per cent are 3.8 to 5.6 per thousand births, both substantially below the summary rates of the Collaborative Study [402].

For example, using data for white Americans only (404, p. 41), the perinatal death rates in cooperating institutions ranged from 23.99 to 43.09 per thousand births, six to eight times the result obtained by Balfour. Nevertheless, biologically, the result has to be accorded sufficient praise for the achievement. It is always more difficult to further change low prevalences of disease, not to mention the gradual loss of skills from infrequent events, a

point which stood behind the plight voiced by Hamlin's students. Despite the narrow range of values, the change itself was a decrease of 38.14 per cent [22].

Balfour also discussed an independent study in which a group of well fed women had 30 per cent less toxemia and a significantly lower prematurity rate than a group of women who were not as well nourished [23]. These results are all the more remarkable when one recalls both reports came from Britain during World War II. The principal work described in the 1942 report began in March 1938 and ended in December 1939, four months after the war began. The 1944 paper reported work performed from early 1937 to March 1939.

Knoblock and Pasamanick noted in the absence of low birth weight, toxemia of pregnancy (defined as the presence of edema, hypertension, and proteinuria) is not significantly associated with major neurological abnormalities, such as cerebral palsy, epilepsy, and mental deficiency [292]. Toxemia, however, was found to be highly associated with the birth of children with minor degrees of cerebral damage, which, during later childhood, frequently become manifest as behavioral disorders or result in specific learning disabilities. They noted that among mothers of infants with a developmental quotient (DQ) under 80 (90% of the infants in the study had DQs between 90 and 120), the incidence of toxemia was twice that of the mothers of the entire study group [292].

Progesterone secretion in toxemic women usually declines, possibly inducing premature labor. Although there is a high association between malnutrition and prematurity (as with malnutrition and low birth weight), the mechanisms by which malnutrition causes prematurity are not all well known at this time. Intrauterine malnutrition may cause premature labor by stimulating the pituitary, which is very sensitive to malnutrition, to release oxytocin [114].

A decrease in uterine blood flow, a direct consequence of hypovolemia, leads to an increase in uterine activity [26]. As the uterine contents enlarge, stretching the myometrium, local synthesis of prostaglandins is stimulated. These hormones promote vasoconstriction and myometrial contracture. Uterine contractions usually follow a substantial decrease in progesterone secretion by removal of the progesterone block which decreases the electrochemical gradient of uterine muscle, reducing its responsiveness to contractile stimuli [112].

INDIRECT EVIDENCE OF ADVERSE EFFECTS OF MALNUTRITION

Autopsies of malnourished infants reveal that besides giving rise to small, infarcted, and otherwise pathological placentas, malnutrition promotes

deficiencies in the number of cells and cytoplasm in various organs of the fetus or newborn [391].

Autopsies were performed on 1,044 consecutive stillbirths and infant deaths at one hospital. Naeye, the chief pathologist for the study (but not of the hospital), excluded infants of the most malnourished mothers by selecting only those in which the pregnancy was not accompanied by toxemia, abruption of the placenta, infections, or other serious complications which are highly associated with inadequate nutrition. The exclusions brought the number for analysis down dramatically, to 467 cases. The dietary intake was distributed as shown in Table 5-15. Body measurements and organ weight records for the 467 deaths were complete.

Table 5-15
DIETARY INTAKE FOR AUTOPSY ORGAN EVALUATION [391]

<i>Dietary rating</i>	<i>Number of cases</i>
1500 kcal diet	75
1200 kcal diet	48
"Standard advice" on salt avoidance	344
Excluded for overt pathology	700

In addition to excluding 67 per cent of the case material, the paper has a plethora of statistical treatments, mainly the use of percentages of *expected weights* from two other major databases on fetal and neonatal organs [216,478]. Moreover, the statistical limits were not identified as to whether they were standard errors of the mean or standard deviations.¹ Data analysis used four asymmetric categories of maternal weight: (1) overweight at the start of pregnancy, (2) underweight at the start of pregnancy with above average weight gain, (3) overweight at start of pregnancy with low weight gain, and (4) underweight at start of pregnancy with low weight gain. The lack of clearly applicable standards for comparison and considerable overlap in the results, including the graphic representations, and the generation *en passant* of "normal" dietary intake by combinations of data revealed by the study, preclude any summary on what the data means pathogenetically. The most interesting results are for category 4, *underweight mothers with low weight gain*, particularly the 4-6th and 6th+ pregnancies, wherein most organs were much underweight, except for the kidneys.

More recently, Naeye et al. have shown that abruption is related to and at least in part caused by poor nutrition [392].

¹ Personal communication from Dr. Naeye indicated these were standard deviations.

Naeye, who believed that substandard prepregnancy weight and inadequate weight gain during pregnancy were proxies for malnutrition, drew various conclusions from this work. Mothers on 1,200-1,500 calorie diets produced infants (>33 weeks gestation) with organ weights and body measurements significantly higher in category 1 than in category 4. It is apparent that the results would have been more useful if infants of the severely malnourished women had been included in the study.

In all four groups, infant cell nuclei were about the same size whether the mothers had been placed on low calorie or regular diets. The liver, adrenals, and placenta weights were found to be most affected by malnutrition. When nutrition both before (crudely estimated by Naeye to be prepregnancy weight plus weight gain) and during pregnancy (as measured by whether a low calorie diet was imposed) were considered, other factors, age, race, the marital status, and interval since the prior pregnancy, whether considered collectively or individually, had no effect on infant size. Naeye attributed the very high number of defective children of low socioeconomic groups to the fact that an extremely high percentage of the mothers were on severely restrictive diets.

Even more indirect and circumstantial evidence strengthens the established relationship between environmental factors and birth weight. Smoking, which decreases the oxygen carrying capacity of hemoglobin because of binding of carbon monoxide, and which can reduce the appetite, has been shown to result in lower birth weights at every gestational age range without having a similar effect on the total length of gestation [2]. Usually, the greater the number of cigarettes smoked during pregnancy, the more significant was the decline in birth weight.

It has been hypothesized that the reduction in birth weight can be caused by hypovolemia in addition to reduced placental transport of oxygen. Nicotine or other components in cigarettes cause vasoconstriction [2]. A reduction in carbonic anhydrase has been observed in the umbilical cord blood of fetuses from mothers who smoke [2]. Even though it can lower birth weight, smoking apparently is not as pernicious as malnutrition during pregnancy, as low birth weight infants born to smokers have a significantly lower neonatal mortality rate than underweight infants born to nonsmokers [2].

High altitude is known to be associated with low birth weight and increased morbidity and mortality. Studies have demonstrated a direct relationship between altitude and incidence of low birth weight [326]. It is interesting to note that the capital of old Peru, Cuzco, was moved from the Andean mountains to Lima at sea level in the seventeenth century because of a high frequency of infertility and neonatal mortality among animals [382].

Lake County, Colorado, where the altitude is between 10,000 and 11,000 feet, has rates of low birth weight, neonatal mortality, and congenital defects which are extremely high, even though its residents are generally of high income status [326]. Over a five-year period, the low birth weight incidence in the county was 30.8 per cent, the highest in Colorado, and significantly higher than that of Denver, a mere mile above sea level (10.4%) ($p<0.00001$). Reductions in body length and head circumference accompanied those in birth weight among the county births [247]. Table 5-16 shows the significant association between altitude and weight at birth.

Table 5-16
RELATIONSHIP BETWEEN GEOGRAPHIC ELEVATION
AND BIRTH WEIGHT [326]

Location	Time Frame	Altitude		Mean birth weight
		Feet	Meters	
Lake County	1949-5	10,000+	3,048	2,655 g
Mexico City	n.a.	7,000	2,134	2,992
Denver County	1953	5,280	1,609	3,035
Los Angeles	n.a.	740	226	3,443

It is noteworthy that no difference in birth weight could be attributed to race or gestational age, which showed no appreciable decrease [326].

Lake County's neonatal death rate for 1,206 births from 1949 through 1953 was 41.6. The rate in Denver was 23.4 during the same period; the difference is significant ($p<0.02$). The incidence of congenital defects in Lake County (1.2%) from 1949 to 1951 was 44 per cent higher than the 1951 rate for Denver and 30 per cent greater than in New York City [326].

A comparison of the birth weights of children born in Lake County with siblings not born in the county revealed a dramatic difference [247]. A total of 120 women who delivered children both in Lake County (261 births) and elsewhere before moving to Lake County (293 births) showed an average birth weight decrease of 290 g in county births. The average birth weight of the children born outside the county was 3,130 g; that of the 261 younger siblings was 2,840 g. In an attempt to determine whether hypoxia caused the high rate of low birth weight, oximetric readings were taken on 99 Lake County women with no complications and health [248]. The readings failed to indicate a relationship between elevation and hypoxia among the women, all of whom delivered at one hospital during the same year. One might speculate whether women with obstetric complications in this setting would have shown important changes in oximeter readings. The singleton infants born to the 99 women showed reduced arterial oxygen saturation very soon

after birth; the values rose to the normal levels within a mean of 14 minutes after birth. Many of these children might have had fetal hypoxia, which was not measured [247]. The effects of cosmic or ultraviolet radiation, reduced humidity, and other factors associated with high elevation may also have important albeit indirect effects on birth weight.

Despite the significance of the data which seem to indicate that smoking and high altitude lead to underweight births, they must be accepted with reservation, as other environmental factors, particularly nutrition, are seldom, and were not in these studies, taken into consideration. It is known that women who smoke considerably during pregnancy frequently give birth to normal and high birth weight babies when they satisfy their increased nutritional needs. Similarly, the possible effects of altitude in decreasing birth weight cannot be fully assessed without considering nutritional status simultaneously. It is possible that the pregnant women in Lake County were inadequately nourished. Without the necessary information, considering the timing of the study, 1949-1951, one cannot rule out the possibility that the prenatal care in the County included salt restricted diets, low calorie diets, perhaps diuretics or other weight control regimens, or appetite suppressants, any of which can reduce birth weight.

Nevertheless, when the mean altitude above sea level of these four communities is plotted on rectangular coordinates against the mean birth weights for each, the result (not shown) is a reasonably tight straight line (a "biological" linear relationship)! This observation alone, not made graphically by the original authors, is strong evidence of a causal relationship between the physiological environment of the air we breathe (viz, the partial pressure of oxygen), and fetal growth. Confounding would come from other factors. Lichy et al. also published results from other cities in Mexico which did not fit so well into the linear pattern, so, given the dates of the actual study, 1949-1953, revisiting this factor is surely in order. On the other hand, it should be pointed out that neither Battaglia and Lubchenco [32] or Lubchenco et al. [342], who published later and from the same city, Denver, took into account effects of altitude on the birth weights of infants in the Denver, Colorado area, which were the basis for the Lubchenco birth weight and gestational age mortality risk chart which was very popular in the 1970s (first edition, p 112). At minimum, some adjustment in the figures would seem proper since Denver birth weights are below those of most of the United States, which is at lower altitudes above sea level. The past twenty years have seen such dramatic advances in neonatology that the particularities of the graphic plot are no longer meaningful and this has been omitted from the present edition.

Prospective and retrospective nutritional studies documenting causal relationships between poor nutrition and developmental disabilities are

valuable. Extensive longitudinal anterospective and retrospective studies of neurological function of children born to women, measured by variables known to be affected by nutrition and likely to have been malnourished, are available. These studies, in which the mothers' nutritional status during pregnancy was unknown or could not be studied retrospectively accurately, do provide useful indication of the effects of maternal malnutrition on mental and physical development when indicators of malnutrition associated with childhood neurological impairment are identified. Prenatal and paranatal factors which are due to malnutrition include low birth weight, gestosis, premature separation of the placenta, and severe maternal and infant infections.

The effect of maternal dietary intake on infant development is indirectly implicated by analysis of seasonal variations of birth weight, complications of pregnancy, and developmental disabilities. Knobloch and Pasamanick showed that women in early pregnancy during the summer months have more mentally retarded children, a greater likelihood of complications, and more low birth weight infants than women not pregnant during the summer [289,411,412,414].

A highly imaginative analysis of the relationship between the incidence of mental retardation and season of birth, conducted by Knobloch and Pasamanick, provided further evidence of known adverse effects of under-nutrition in utero [289]. They demonstrated that infants born during winter had a substantially greater chance of being mentally retarded than infants born during summer months.

Showing the relationship between mental deficiency and season of birth was not affected by summer encephalitis, they disproved the theory that mental retardation was in large part caused by infections [289]. There was no increase in the incidence of mental retardation (as measured by admissions to a state hospital for the retarded) which could be attributed to a major pandemic of influenza [412]. Instead, they attributed the excessive number of mentally retarded children born during the winter to the fact that among winter births the time of initial glial proliferation occurs during the summer, when protein/calorie intake is likely to be low, and salt loss is likely to be substantial [412]. As previously discussed, glial growth and development can be markedly impaired by inadequate maternal nutrition.

These authors examined the birth records of all infants born between 1913 and 1948 (excepting 1946, when inadequate records were kept) who had been admitted to one large state school for the mentally deficient [289]. Since the youngest children admitted during any calendar year were at least six years of age, it is unlikely that the month of birth was a factor in consideration of admission *per se*. Since no other mechanical factors could conceivably

cause the date of admission to the institution to be influenced by the date of birth, the month of birth among those admitted would be expected to be distributed uniformly. For the years considered, there were over 450 admissions for each month of birth, a sizable data base.

Knobloch and Pasamanick discovered that the five months with the highest rates of admission (ratio of admissions to number of state births) were November through March. In contrast, the lowest rates occurred from June through October. These differences were not accounted for by socio-economic factors, which are known to be associated with mental retardation. On the contrary, there was a slightly higher birth rate during the winter months for the higher socioeconomic groups than for those of lower socioeconomic status.

The highest monthly rate of admission (in February) was 16.2 per cent higher than the lowest rate, which occurred in August, the seasonal counterpart of February. In addition, the admission rate for births in the first three months of the year was 9.4 per cent higher than for births of the seasonal counterpart (July through September). Both of these differences were significant at the 2 percent level.

It is notable that infants born in February, the critical time for differentiation of the cerebral cortex, which occurs from approximately the eighth to twelfth weeks of gestation, is the previous July, during which the intake of essential nutrients, especially calories and protein, is more likely to be low. The authors noted that salt depletion, expected to occur during summer months, may be as important a factor in causing impaired cerebral cortical differentiation during the third month of gestation as a reduction in protein intake [289]. Hypovolemia due to sodium depletion and hypoalbuminemia from poor protein intake can retard cellular differentiation, which is highest during the third fetal month [414].

Knobloch and Pasamanick theorized if a reduction in essential nutrients were the major factor contributing to the extremely high number of mentally deficient children born during winter months, the incidence of mental retardation would be highest in the winter months during the years with the hottest summers [289].

Consequently, they compared the monthly rate of admission to the state mental school according to the period corresponding to the eighth to twelfth weeks of gestation for the years with the hottest summers with those with the coolest summers. For the years 1913 through 1945 and 1947 through 1948, temperature records were examined and the data averaged for the six largest cities in Ohio.

The rates of admission during the years when the mean summer temperature was above the median were compared to the years below the median.

The authors discovered that the hotter the summer during the 35 year period, the greater was the incidence of mental retardation the following winter. Equally revealing, mild summers were not followed by an increase in the incidence of retardation the following winter.

Although, as Table 5-17 suggests, there was no significant temperature differential in the rate of admission of those with mental deficiency when the month of June corresponded to the eighth to twelfth weeks of gestation, the rates of July and August showed highly significant differences.

Table 5-17
RATES OF ADMISSION FOR MENTAL DEFICIENCY BY MONTH
OF BIRTH ACCORDING TO MEAN TEMPERATURE DURING
THE 8TH THROUGH 12TH WEEKS OF PREGNANCY [289]

<i>Months</i>	<i>Rate per 1000 births for years with mean temperature above median</i>	<i>Rate per 1000 births for years with mean temperature below median</i>
June	1.402	1.411
July	1.658	1.276
August	1.519	1.206
July-August	1.5885	1.241

The admission rate of offspring from women at 8 to 12 weeks of gestation during June, July, or August was significantly higher during the hotter summers than the cooler summers. The fact that this difference, which would occur by chance in less than 1 in 1,000 cases, is more significant than the differences between month of birth and month of admission (as examined earlier), lends additional weight to the concept that dietary deficiencies, which are likely to occur during periods of warm temperatures, account for many instances of mental deficiency during times of critical brain growth. The 23 per cent higher rate of admissions for children who were at 8 to 12 weeks of gestation during those years in which July was unseasonably hot than during years in which July was more mild is nearly 2.5 times as great as the ratio of the rate of admission during the first quarter of the year to that of the third quarter.

The narrow difference for the month of June indicates an even sharper seasonal effect. As a result of these findings, Knobloch and Pasamanick hypothesized that the incidence of complications of pregnancy, especially toxemia, are also temperature dependent, as is mental deficiency [289]. Taking a 10 percent systematic sample of live births in New York City in 1956, they determined that complications of pregnancy are related to the season of birth [411]. There was a significantly greater incidence of one or

more complications of pregnancy among births during the first three months of the year than during the seasonal counterpart, July through September ($p<0.001$). The incidence of gestosis was the complication most significantly related to season of birth. Other complications did not show as high an association [414].

They believed that inadequate maternal dietary intake, which is likely to be abnormally low during summer months, accounted for the higher incidence of complications during winter births, which are especially vulnerable to seasonally induced malnutrition [411]. As in their study of season of birth of the mentally deficient children [410], they concluded that since the critical period of organization of the cerebral cortex occurs at approximately two to three months fetal age, a nutritional deficiency can lead to direct fetal effect along with possible effects on the pregnancy itself.

Chapter 6

BIRTH WEIGHT AND DEVELOPMENT

NUMEROUS REPORTS well document the association between birth weight, which has been shown in earlier chapters in this book to be a function of maternal nutrition, and childhood mental and physical development. Several well-controlled studies exemplifying this association between low birth weight and neuropsychiatric and physical disorders will be reviewed in this chapter.

The highly significant relationship between poor maternal nutrition and infant neurological dysfunction has tremendous public health implications when one considers neurological abnormalities diagnosed in early life are highly predictive of subsequent, often permanent, central nervous system impairment [295]. Up to 40 per cent of low birth weight children have diagnosable neurological disorders by age seven years [464].

Two notable studies documented high correlations of early life neurological assessments with those of later childhood [288,295]. In one, infants from sixteen weeks to one year of age were given a complete Gesell Developmental and Neurological Examination. Despite being in a hospital-based child development program, many were found by testing to be normal. At ages from six to ten years, the children were asked to take a battery of 12 tests to reevaluate neurological function. One hundred and twenty-three children, for whom complete socioeconomic data were available, took the series of exams, which independently and collectively have been considered as diagnostic of brain damage.

In addition, a standard neurological examination was done by a pediatrician who had not previously seen any of the children.

The diagnosis of definite neurological damage during infancy was highly predictive of the presence of such impairment more than five years later. The

correlation of test results from infancy and those administered in later childhood was 0.70, very significant statistically. As might be expected, it was found the correlation between the test scores was lowest among those who had the highest developmental quotient (DQ) during infancy.

Another study was designed to test reliability of tests to assess neurological function in infancy. Fifty-four infants from the previous study were examined initially during the same year, and compared to 28 controls, all *assumed* to be normal [295]. The test results were controlled for race and socioeconomic status. Of these infants, 30 were normal and 24 were found to be abnormal. Table 6-1 shows results of tests given in late childhood (from ages 6 to 8 or 9 years) to assess neurological function were found to be highly correlated with scores obtained during infancy, an overall predictive rate of 94 per cent. The correlation of the two sets of exams with twenty three variables was 0.87 ($p<0.00001$).

Knobloch and Pasamanick estimated low birth weight alone was responsible for 35 per cent of the neurological impairment. They concluded that other complications which predispose to neurological impairment were also basically preventable. They declared: "Prematurity, bleeding, and toxemia can almost be eliminated by the high protein and vitamin diets of any prenatal care program of superior quality [288]."

Table 6-1
RELIABILITY OF ASSESSMENT OF
NEUROLOGICAL FUNCTION IN INFANCY [295]

Category	Number	Per cent infant test matched test as child
Unscreened controls	28	100.00
Screened normals	30	96.67
Screened abnormalities	24	83.33

RETROSPECTIVE AND ANTEROSPECTIVE STUDIES

Studies of twins, especially monozygotic twins, by providing intrinsic controls of most genetic and some environmental factors, generate significant relationships between birth weight and mental and physical health. Babson et al. examined performance and development records of dissimilar size twins born between 1950 and 1958 [15]. Sixteen sets of twins, nine monozygotic, were selected so the smaller twin weighed less than 2,000 g and *was at least 25 per cent less* than the larger twin at birth. The average birth weight of the 16 smaller twins was 1.61 kg; the larger twins had a mean weight of 2.47, a difference of 860 grams. Tests, such as IQ, vocabulary, and language, and

height, weight, and head circumference measurements were taken at ages ranging from 4.5 to 11 years. None of the trained examiners in this anteretrospective study knew any birth weights.

Four smaller twins (25%), all monozygotic, had physical defects, whereas no larger twin had physical disorders. Four of the smaller twins (25%) had higher and ten (62.5%) had lower IQs. When examined, at ages six to nine years, the smaller twins at birth had measurements of height, weight, and head circumference which were significantly lower, as a class. Not all pairings kept this overall pattern. For both height and weight, the smaller twin was larger in three cases (18.75%) and smaller in 11 cases (68.75%) but only one (6.25%) had larger head circumference than the higher birth weight twin (this child was also taller and heavier); in 14 of 16 cases (87.5%), the larger at birth twin had the greater head circumference in childhood. Table 6-2 summarizes the results of the examinations of these sixteen sets of twins. Overt presence of twin transfusion syndrome (parabiosis [485]) was not noted. Growth discordancy occurs in average or appropriate size nonparabiotic, term twin sets [45].

Table 6-2
ASSOCIATION OF BIRTH WEIGHT OF SETS OF TWINS
WITH VARIOUS TESTS AND MEASUREMENTS [15]

<i>Examination</i>	<i>Mean difference between larger and smaller twin</i>	<i>Significance</i>
Vocabulary	Score of 2.5	None
IQ	6.75	0.05
Height	4.34 cm	0.01
Head circumference	1.34 cm	0.001
Weight	3.95 kg	0.001

Table 6-2 suggests that vocabulary, a feature of intelligence, was not measurably different with respect to birth weight but further analysis of the twins revealed a subtlety to the matter.

The differences were more dramatic between the nine paired monozygotic twins, as shown in Table 6-3. Neither size at birth nor mental and physical development was significantly related to birth order (nine smaller twins were born first) within the monozygous twin pairs. There were no differences between the higher and lower birth weight twins with respect to neonatal complications which could account for differences in the tests and measurements [15]. Babson et al. found more differences in language and intelligence than in motor aspects of speech and articulation in this subset and concluded that birth weight and head circumference accounted for major functional differences in intellectual potential.

Table 6-3
ASSOCIATION OF BIRTH WEIGHT WITH VARIOUS
TESTS AND MEASUREMENTS, MONOZYGOUS TWINS [15]

<i>Examination</i>	<i>Mean difference between larger and smaller twin</i>	<i>Significance</i>
IQ	6.56	0.05
Head circumference	1.67 cm	0.01
Weight	4.81 kg	0.001
Height	5.89 cm	0.001

These are rather remarkable results despite the small size of the sample. Discordancy in fetal growth and phenotype of anomalies in monozygous twins, which includes fused twins and parasitic acardiac fetus, are well known to specialists in the field [21] but perhaps less so to the general medical community.

Zitrin et al. compared the birth weights of 370 12-year-old children under psychiatric treatment with 370 controls [579]. The prevalence of low birth weight was much higher ($p < 0.005$) among the patients (14.1%), compared to controls (7.8%). Between the study and control groups, there was no difference in either previous fetal loss or parental age, supporting a likely association between low birth weight and mental abnormality. This is further supported by the belated finding of Susser and Lin on hospitalization rates for overt schizophrenia of the cohort born in Holland from the maximum effect of the Dutch starvation incident [517].

Organic brain damage was much more frequent among the low birth weight children in the 370 study group children. Among the schizophrenics, there were more low birth weight infants in the study group. Zitrin's observation about low birth weight and schizophrenia is comparable to that of Pasamanick and Knobloch, who found an increase in schizophrenia among children born after hot summers in comparison to births following cool summers [414]. As mentioned in Chapter 5, fetal undernutrition is more likely during unseasonably hot summers than during mild summers or other seasons. Lubchenco et al. designed an anterospective study over a 2.5-year period of 187 infants, none weighing more than 1,500 g at birth. They were admitted to the same infant center [342]. Infant mortality was 49.7 per cent, typical for the late 1940s and early 1950s, the time frame of births in the study. There were 94 surviving infants and 63 of these were available for medical, neurological, psychological, electroencephalographic (EEG), and ophthalmological tests, all of which were given at approximately ten years of age. There was no control group, but the high percentage of abnormalities observed indicates that birth weight $\leq 1,500$ g is significantly associated with

permanent handicapping conditions.

Twenty-six of the 63 children (41.27%) were below the tenth percentile for weight; 30 were below the tenth percentile for height (47.6%). Abnormal EEGs (60.3%) occurred ten times more often than is usual in children born at term.

Forty-three (68.3%) of the children were handicapped; 31(49.2%) had central nervous system disorders. Of these 31, 22 had spastic diplegia; most of the other nine had intellectual impairment. Twenty-five of the 60 children (41.67%) tested for IQ scored under 90. Eleven of these 25 children repeated the first, second, or third grades, and some had to repeat more than once. Meanwhile, 20 of the 35 children with an IQ ≥ 90 experienced, the IQ notwithstanding, substantial difficulties in school. Over half of these children had significant emotional trouble or behavioral abnormalities.

Twenty (31.7%) of the 63 children had serious eye defects; seven were blind. The authors attributed some visual impairment to the fact that many of the children were exposed to 60 per cent oxygen soon after birth, implying development of retrorenal fibroplasia [285].

Twenty-six (41.3%) of the children had multiple handicaps. Twenty were classified as "normal (31.7%)," but many of these had minor mental or psychological difficulties.

Birth weight is both more accurate and precise than length of gestation and is more predictive of infant morbidity and mortality. Consequently, various studies in which birth weight is used as an independent variable are reviewed here. Lubchenco et al. found birth weight is a better predictor of neonatal mortality than the length of gestation [343]. The mortality rate of newborns weighing $<2,000$ g at birth was found to be several times more than of infants whose birth weight was $>3,000$ g. These were data from the period prior to the widespread impact of neonatal intensive care units, specifically July 1, 1957 through July 1, 1969, representing the "raw data" baseline [32,343], despite the lack of accounting for the mile high altitude of greater Denver. The first edition of this book included a copy of the Lubchenco-Battalgia graphic; this is now obsolete for the reasons noted and has been dropped from this edition.

Drillien, in a study of 49 school-age children weighing no more than 1,360 g at birth, all born at two hospitals, demonstrated a very large number had mental, physical, or behavioral handicaps, often in combination [151]. Many of these children, all at least five years old at the time of the study, were relatively ineducable in regular schools. The socioeconomic status of the families was quite varied; 37 per cent were graded as middle class, 37 per cent as working class, and 27 per cent as the lowest economic class.

Twenty-six (53%) had one or more physical defects; six (12%) had cerebral

palsy. Seventy-nine per cent were said to have one or more behavioral problems such as lack of concentration, insecurity, immaturity, nervousness, shyness, passiveness, and aggressiveness. It is noteworthy that twenty-four (49%) were so mentally or physically handicapped they were unable to be educated in a regular curriculum. Five (10%) were so severely handicapped they received no formal education; nine others attended special schools for the physically handicapped. Moreover, 13 of 25 in attendance at regular schools were provided additional special education. Only one out of 49 children had an IQ >109 and 34 (69%) scored below 90.

Drillien also studied growth and development in 71 out of 85 surviving low birth weight children available for a series of test procedures [150]. These children, all weighing <1360 g at birth, were from two to nine years at the time of study.¹ The real age of each child was used in calculating acceleration or retardation in growth and mental development (i.e., chronological age minus weeks of prematurity).

Despite this adjustment, physical and mental handicaps were as pronounced as in the other reports by Drillien [147-152]. A major physical handicap afflicted 16 of the 71 children. Quite revealing was the high rate of intellectual deficiency among these low birth weight children. Only nine children were considered to have average or above average intelligence (12.7%). Moreover, 14 per cent had IQs <70, and 49 per cent had IQs between 70 and 85 (Table 6-4). Twenty-seven per cent needed special schooling because of mental or physical handicap.

Table 6-4
DISTRIBUTION OF IQ IN 71 LOW BIRTH
WEIGHT CHILDREN (<1360 GRAMS) [150]

<i>IQ rating</i>	<i>Children</i>	<i>Per cent</i>
<70	10	14.1
70-85	35	49.3
86-100	21	29.6
>100	5	7.0

Four IQs were rated at exactly 100.

Severe growth retardation was also pronounced. Among the 70 children whose weight was known, 88.6 per cent were below expected weight for age. Seven children weighed *only half* expected median weight for age. There was no tendency for improvement with age: undersized children were a constant share from age 2 to 9 years.

¹ Drillien's paper suggests overlap between some of the studies but offered no means by which to identify the links. All six papers are a valuable resource, the noted limitations notwithstanding [147-152].

A later paper noted seven pairs of twins [151]. Both twins in three sets were 1360 grams or less at birth; one twin in each of the other four sets weighed more than 1360 g and was excluded from Drillien's test sample. The smaller twin in the three sets with dual low birth weight tended to be more handicapped, scoring lower on the IQ test [151]. Nevertheless, comparisons amongst the excluded twins are of interest (Table 6-5).

Table 6-5
FINDINGS IN SEVEN TWIN PAIRS WITH AT LEAST ONE TWIN \leq 1360 GRAMS AT BIRTH [151]

Twin birth weight (g)			IQ Score		
Larger	Smaller	Difference	Larger	Smaller	Difference
<i>Both twins \leq 1360 grams</i>					
1275	1162	113	95	85	10
1360	1247	113	67	67	0
1360	1191	169	56	43	13
Average weight, larger twin: 1314 g; smaller twin: 1200 g; difference = 114 g.					
<i>Only one twin \leq 1360 grams</i>					
2325	1247	1078	107	80	27
1871	1360	511	110	91	19
1559	1275	284	100	82	18
1531	1332	199	n.a.	87	n.a.

Average weight, larger twin: 1821 g; smaller twin: 1304 g; difference = 517 g.

In general, the smaller twin of all seven sets tended to have more severe mental and physical impairment. The difference in birth weight was progressively greater as the birth weight of the larger twin rose, as might be expected; birth weights are closer together as one passes down the weight scale. At the same time, a graphic plot of the data (not done by Drillien) shows a more remarkable feature (Figure 6-1): there is a linear relationship between the birth weight of the larger twin and the *difference* between twins (Figure 6-1) which is not found between the smaller twin and the difference in weights (data not shown). In addition, there is a good correlation (again, not graphed or reported by Drillien) between the difference in birth weights and the difference in IQ (data not shown). Also, in general, the correlations are better at the higher birth weights: those under 1500 grams (for the larger twin) and those under 1250 grams (for the smaller twin) show more variation.

The variation in the IQ scores reported by Drillien [151] is reduced when another interesting feature of the study is examined closely: seven *unpaired* twins weighing from 926 to 1304 grams (mean = 1098.6 g) with IQs in the

Difference in twin weight by weight of larger twin

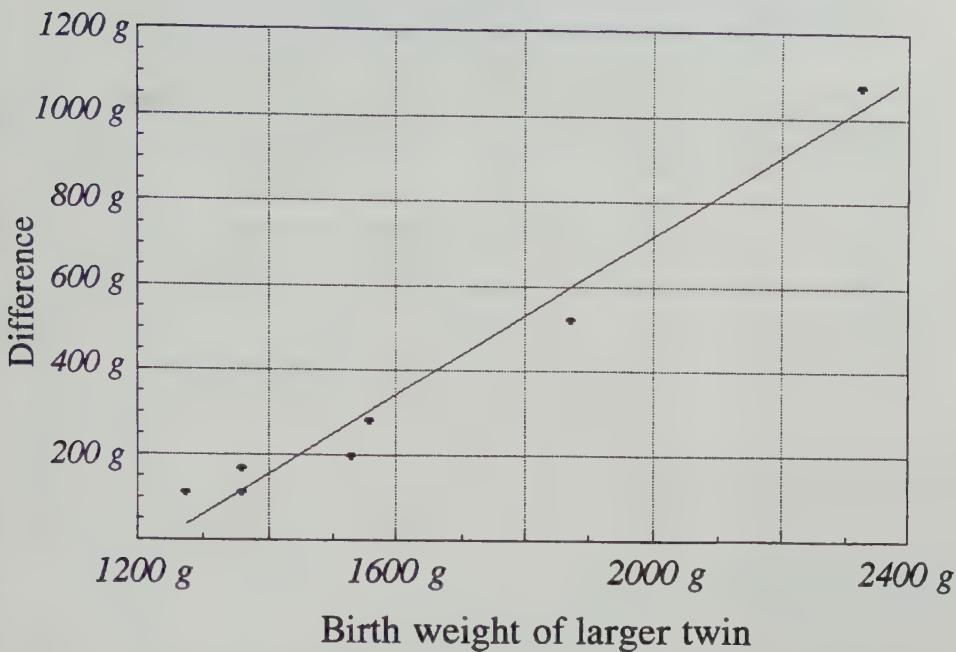


Figure 6-1. Growth of twins tests the biological limits of nutritional supply. The difference in birth weights in a twin pair is directly related to the growth achieved by the larger twin (and inversely related to the mass of the smaller twin), an expression of their combined growth limit.

range of the smaller *paired* twins. When combined as samples of extreme low birth weight due to twinning, a good correlation results between birth weight and IQ. A similar combination of the unpaired twin and the paired larger twin data leads to a remarkably similar result, as do all combinations of twins from Drillien's database as independent individuals (Table 6-6). The comparable regression for the 22 singleton births with measured IQs is in Table 6-6 as well.

The slightly steeper regression slope of the smaller paired twins with the unpaired twins, if superimposed on the other plots, is mildly suggestive of a curvilinear function in which IQ declines more rapidly below birth weights of about 1000 grams. When these are plotted together (Figure 6-2) a superimposed regression line highlights the greater likelihood of a sigmoid or exponential plot across the middle range which indicates a narrow birth weight zone with diverse results in measured IQ, 1000-1400 grams and IQ scores at 55-95. This birth weight zone is very critical and a major factor in adverse neonatal and infantile outcomes *per se*. Drillien's data are thin at this

Table 6-6
LINEAR REGRESSION FORMULAS BETWEEN BIRTH WEIGHT (BW)
IN GRAMS AND IQS, BY VARIOUS GROUPINGS OF TWINS,
AND SINGLETONS [RECALCULATED FROM 151]

<i>Grouping</i>	<i>Number</i>	<i>Total</i>	<i>Linear regression equation</i>
Unpaired + Smaller paired twin	7	14	$IQ = (0.0578 \times BW) + 3.47$
Unpaired + Larger paired twin	7	13	$IQ = (0.0389 \times BW) + 25.16$
Unpaired + Larger and smaller paired twins	6	20	$IQ = (0.0398 \times BW) + 24.74$
Singleton births	22		$IQ = (0.0397 \times BW) + 37.16$
All low birth weight	42		$IQ = (0.0325 \times BW) + 40.29$

point, but her overall material is the best available under the conditions surrounding her effort: an absence of confounding neonatal interventions, good consistency of observation, and full access to the subjects, all matters very difficult to replicate at our end of the 20th century.

Several important *biological* principles come from these cases. *First*, the difference in twin weight depends on the weight of the larger twin. *Second*, twin order by weight or birth, absent any further specific obstetric factor which might amplify injury to the fetus or newborn, is irrelevant to intellectual capacity. And, *third*, the mid-childhood IQ is directly proportional to the birth weight in *low birth weight infants*. Obviously, at the opposite end of this complex function, enormous birth weight does not imply (or guarantee) extremely high intelligence. There is, then, a biologic limitation, on brain growth and maturation. The parametric link is a function, perhaps, of a gestationally-related third factor which is satisfied at some (yet to be determined) point in maturation of the brain, beyond which the body lays down tissue mass everywhere without an effect on basic cerebral architecture. In a way, this is reminiscent of limitations found by Rosso on fetal body weight referent maternal weight gain (proxied by *postpartum* weight) [460].

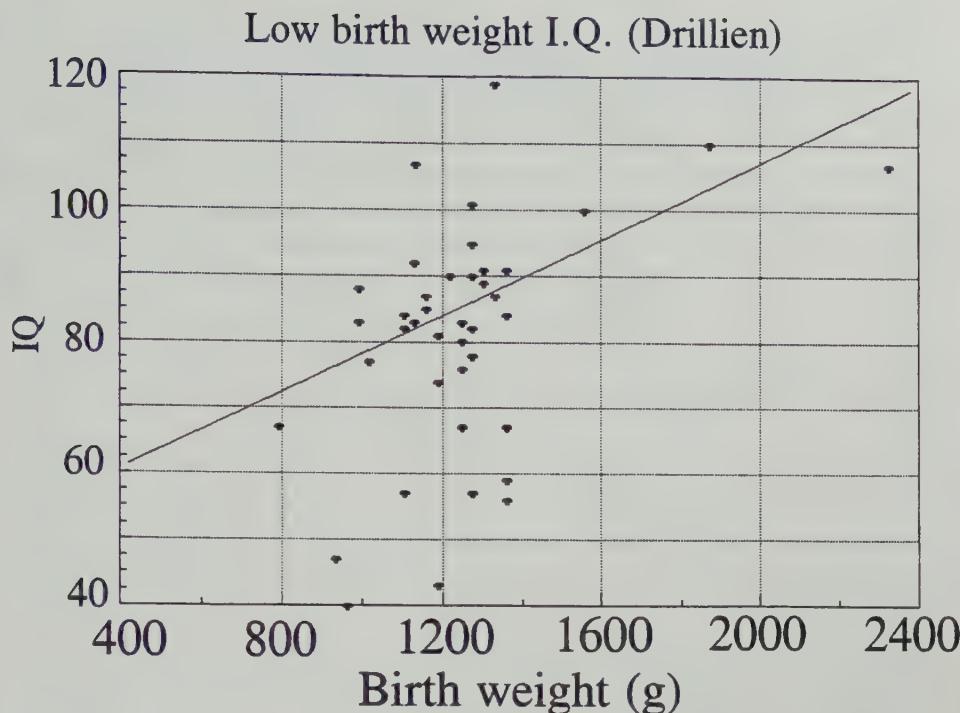


Figure 6-2. Linear regression may yield the wrong interpretation. The thin regression line suggests correlation between birth weight and subsequent IQ. The cluster of IQ scores for birth weights 1000-1400 grams may actually delineate a threshold effect.

Drillien compared the developmental status of 30 children from this study with siblings other than the twin: 73 per cent of low birth children were markedly more handicapped than their siblings; only 7 per cent showed superior development [151].

Drillien compared IQ scores of 49 low birth weight children with 92 random controls from the same hospital [151]. The controls all weighed >2,268 g at birth and were tested earlier [151]. Controls were biased toward above average intelligence. Drillien gave no explanation of this result nor of the randomization method.

For each economic class, the IQ scores were lower in the low birth weight group. As Table 6-7 shows, IQ scores of 11 of the low birth weight children were lower than any of the controls. The table reflects the strong tendency of British workers of the period to express developmental results in terms of socioeconomic classes, and the table has been preserved as Drillien reported. It would have been more meaningful if controls had been chosen such that the three economic classes would have been more equal in size. Internal

Table 6-7
INFLUENCE BETWEEN BIRTH WEIGHT ON THE ASSOCIATION
BETWEEN IQ AND THREE SOCIOECONOMIC CLASSES [151]

IQ	Control group			Low birth weight group		
	Middle	Working	Lower	Middle	Working	Lower
<60				1 (5.6%)	1 (5.6%)	4 (30.8%)
60-69				0	4 (22.2%)	1 (7.7%)
70-79	0	1 (2.9%)	1 (9.1%)	2 (11.1%)	0	2 (15.4%)
80-89	1 (2.1%)	2 (5.9%)	3 (27.3%)	5 (27.7%)	8 (44.5%)	6 (46.1%)
90-109	10 (21.3%)	20 (58.8%)	6 (54.5%)	9 (50.0%)	5 (27.7%)	0 (46.1%)
>109	36 (76.6%)	11 (32.4%)	1 (9.1%)	1 (5.6%)	0	0
Totals	47	34	11	18	18	13

distribution across the intelligence scale might then have shown the effect of low birth weight [151]. Nevertheless, by Drillien's account, only 2.2 per cent of the controls had an IQ <80 versus 30.5 per cent of low birth weight children ($p<10^{-6}$).

A partially overlapping controlled study on approximately 400 low birth weight children showed birth weight to be inversely correlated with a need for special education [58]. Of infants weighing $\leq 1,586$ g at birth, 21.1 per cent needed special education as a result of mental deficiency, in contrast to 6.9 per cent for birth weights between 1,586 and 2,040 g. Both rates are much higher than the prevalence in Scotland of 1.9 per cent at the time. The rates for the need of special schooling for any handicap were 29 per cent for the lowest birth weight group and 10 per cent for those with birth weights between 1,586 and 2,040 g. The concurrent rate for all births in Scotland was 3 per cent.

A subsequent extensive anterospective study by Drillien of 648 infants born between 1953 and 1960 documented relationships between birth weight and IQ, education level attained, and childhood behavior [152]. All of the 52 children born after 1956 weighed $\leq 1,360$ g at birth. Multiple births accounted for 38 per cent of cases and 14 per cent of the children died before the age of seven.

During administration of IQ and behavioral tests, examiners were not aware of the birth weights of any child. At the time of the study, 53 seven-year-old children and 461 eleven- to thirteen-year-old children were tested for definite handicap. Many of the original 648 infants died or could not be followed. Only 1 per cent of infants weighed $>2,500$ g at birth had moderate to severe mental, neurological, or physical handicaps. In contrast, 64 per cent of infants with birth weights $<1,254$ g were afflicted similarly. Table 6-8 indicates a near linear relationship between birth weight and moderate or

severe impairment. Assuming the data and design of the study are reliable, the probability birth weight is *not* related to mental, neurological, and physical impairment is less than one in a billion.

Table 6-8, which lists the percentage of children with certain handicaps by various birth weights, the category moderate or severe denotes children with cerebral palsy, mentally retardation, or who were ineducable in regular schools. In general, children with mild handicaps had an IQ between 70 and 79 plus those with marked behavioral difficulties by age eleven years. Percentages for each birth datum are in parentheses.

Table 6-8
ASSOCIATION BETWEEN BIRTH WEIGHT
AND RISK OF HANDICAP (514 CASES) [152]

Birth weight	Number	Degree of handicap		
		Moderate or severe	Mild	Little or none
≤1250 g	36	23 (64%)	6 (17%)	7 (19%)
1251-1500 g	47	16 (34%)	10 (21%)	21 (45%)
1501-1750 g	26	5 (19%)	6 (23%)	15 (58%)
1751-2000 g	67	8 (12%)	20 (30%)	39 (58%)
2001-2250 g	57	2 (4%)	13 (23%)	42 (74%)
2251-2500 g	116	3 (3%)	19 (16%)	94 (81%)
≥2510 g	165	2 (1%)	20 (12%)	143 (87%)
Totals	514	59	94	361

For all socioeconomic classes, IQ increased as birth weight increased (Tables 6-9 and 6-10). Table 6-9 gives the distribution of IQ of 301 of the children as percentile by socioeconomic class. The allocation of "standard" percentile was based upon the IQ scores of children weighing >2,500 g at birth (data not shown). If there were no association between birth weight and IQ, the expected distribution, of course, would be 25 per cent for the lowest quartile, 50 per cent for the middle two quartiles (26th to 75th percentiles), and 25 per cent for the highest quartile.

Despite rather small numbers, the low birth weight infants in every socioeconomic class accounted for far more than the expected number of children with an IQ in the lowest quartile and far fewer than expected for IQs in the highest quartile.

The birth weight effect is seen dramatically by the range of allocation to the lowest quartile, across all six weight scale and socioeconomic class matrix boxes: 36 to 64 per cent. It has no specified biological meaning, as far as can be found in Drillien's data, but the average of these six allocations is actually

Table 6-9
INFLUENCE OF BIRTH WEIGHT ON DISTRIBUTION
OF IQ SCORES BY SOCIOECONOMIC STATUS [152]

Socioeconomic class	Percentile IQ	Birth weight	
		≤2000 g	2001-2500 g
Middle	≤25th	29 (55%)	26 (39%)
	26th-75th	19 (36%)	29 (44%)
	≥76th	5 (9%)	11 (17%)
Total		53	66
Working	≤25th	29 (64%)	28 (36%)
	26th-75th	11 (25%)	37 (47%)
	≥76th	5 (11%)	14 (18%)
Total		45	79
Lower	≤25th	14 (52%)	15 (48%)
	26th-75th	12 (44%)	14 (45%)
	≥76th	1 (4%)	2 (6%)
Total		27	31

49 per cent. Thus, low birth weight accounts for about half of the mental impairment in the overall study. At the other end of the scale, the range of allocations to the upper quartile were from 4 to 18 per cent, with an average of 10.83 per cent. A similar calculation for the middle two quartiles yields a mean of 40.17 per cent which agrees with the other two data treatments. The great middle range is diminished by 20 per cent, and the upper quartile by 60 per cent. This shift of intellectual capacity, as measured by IQ tests, is staggering, and a powerful indictment of low birth weight as the relevant factor for most, if not nearly all, such cases.

No distinction based on birth weight (≤ 2000 vs. ≥ 2001 grams) is in data for the lowest socioeconomic class (ratio: ≤ 2000 g/ ≥ 2001 g = 1.08). The other socioeconomic groups did have a distinction: the ratios were 1.41 and 1.77 for the middle and the working class infants, respectively. This justifies the further conclusion that general environmental factors beyond those measured by birth weight are likely relevant. As emphasized in Chapter 5, birth weight is a powerful proxy for protein and general nutritional status, yet, there are other factors at work, no doubt, including some yet to be identified and characterized.

Even after excluding children with moderate or severe handicaps, a significant correlation between birth weight and IQ at ages 11 to 13 years was found. Table 6-10 shows average IQ scores by birth weight for children attending regular schools.

Table 6-10
RELATIONSHIP BETWEEN MEAN IQ AND BIRTH WEIGHT
BY SOCIOECONOMIC CLASS, AGE 11-13 YEARS [152]

Birth weight	Socioeconomic class					
	Middle		Working		Lower	
	Number	IQ	Number	IQ	Number	IQ
≤1500 g	19	95.3	12	88.2	13	84.2
1501-2000 g	30	101.5	27	94.9	14	84.4
>2500 g	75	110.5	53	100.1	26	90.4

Drillien did not explain why birth weights between 2001-2500 g were not made part of this table (Table IX, p. 566 in Reference [152]).

This is the most difficult [152] of the three principal cited papers from Drillien [150-152] in which to track the cases across the rather wide ranging discussion. Table 6-11 conveys the net of cases for which level of education had been assessed simultaneously by social class and birth weight.

Table 6-11
ASSOCIATION BETWEEN BIRTH WEIGHT, SOCIOECONOMIC STATUS, AND EDUCATIONAL ADVANCEMENT [152]

Socioeconomic class	Number of children	Ineducable		Advanced education	
		Number	Per cent	Number	Per cent
<i>Birth weight ≤2000 g</i>					
Middle	54	4	7.4	13	24.1
Working	43	9	20.9	4	9.3
Lowest	29	8	27.6	0	0.0
<i>Birth weight >2500 g</i>					
Middle	83	0	0.0	38	45.6
Working	55	1	1.8	4	7.3
Lowest	26	0	0.0	1	3.8

Table 6-11 makes clear that satisfactory birth weight, defined as >2,500 g, effectively eliminates a state of ineducability, socioeconomic class notwithstanding. Once again, this is a unilateral effect. At the upper echelon of schooling, social class and higher birth weight combine to enhance learning experience and exposure of middle class children [152]. In fact, there is a rough gradient in Drillien's data on this point.

Behavioral tests were administered to 432 eleven-year-old children. In general, the prevalence of behavioral disorders increased as birth weight decreased (data not shown).

Drillien concluded:

The incidence of moderate or severe handicaps increases with decreasing birthweight, particularly at weights of 2000 grams and under . . . Low birth-weight children were less likely to be selected for courses requiring a higher level of academic competence than were heavier children from similar types of homes. Mean IQ scores . . . fell with decreasing birthweight in all social groups . . . There is no evidence that low birth weight children "catch up" as they become older. [152]

There are several points at which recalculations from original raw data enhance and extend Drillien's general conclusions. These have been provided here as a baseline for possible future consideration of the consequences of modern neonatal intensive care, the extent to which, if any, brain development, neuromuscular function, and mental competency are compromised when equally immature infants are enabled to survive. They surely do so in larger numbers in part because there are more of them and they do so more often as ways are found to overcome the compelling pathophysiology of low birth weight. This is so in spite of the intrinsic hazards of many methods of treatment and maintenance. Other recalculations of the data obtained by Drillien, and that of many others. These pioneers worked at a time when much of what could be done was more in line with descriptive natural history of disease than in rational treatment based on a firm grasp of what the capacities are of the low birth weight child at critical steps in late intrauterine and all of the postnatal journey to later childhood, and beyond.

In a study of 56 sets of twins, Churchill found that IQ was significantly associated with birth weight [103]. The results are meaningful although the sample was selected because at least one twin was attending a psychological clinic. Six of the 56 sets of twins, from 5 to 15 years old at time of study, were excluded from the study because at least one twin had an overt neurological abnormality conceivably affecting the test score. As confirmation of Drillien [150-152], in all six excluded cases, the severely retarded child had the lower birth weight.

All 100 children were given the *Wechsler Intelligence Scale for Children* (WISC) series of exams. Psychologists administering the test had no knowledge of any birth weight or related factors. To increase the reliability of the data, given sets of twins were tested on the same day. The mean WISC full-scale IQ was 81.9 among the heavier twins and 78.6 among the lighter twins.

Greater differences in the results were evident among the 22 sets of identical twins. For these children, the heavier twin weighed an average of 260 g more at birth and had significantly higher scores than their counterparts ($p < 0.001$).

Because the study controlled for genetic factors influencing the full scale IQ, Churchill concluded,

These findings favor the inference that non-genetic causes of low-grade or clinical mental defect, as seen in the discordant, monozygous pairs, are commonly expressed in low birth weight either secondarily to prenatal growth or as a factor predisposing to birth injury. [103]

Churchill's findings in his study of twins were confirmed in an analysis of birth weight of 51 mentally retarded children, all at least six years old at time of study [104]. These children had "undifferentiated" mental retardation, i.e., $IQ \leq 80$, with complete birth records, and were available from those attending a special education class in a middle class school district. A control group was obtained by selecting children in the same school with $IQ > 110$ (the average IQ was 114). The controls were matched with the retarded children for sex, age, and area of residence. As expected from study design, there were no significant differences in sociocultural factors between the study and control groups.

Birth weight was related to IQ at the 0.002 level. Even when cases of low birth weight and prematurity (births less than 38 weeks of gestation) were excluded, differences in birth weight between the study and control groups were nearly as significant. In Table 6-12 the level of significance is given in parentheses.

Table 6-12
RELATIONSHIP BETWEEN IQ AND BIRTH WEIGHT IN
51 RETARDED CHILDREN AND 51 MATCHED CONTROLS [104]

	<i>Average IQ</i>	<i>Average birth weight</i>	<i>Average birth weight (exclusive of low birth weight cases)</i>
<i>Males</i>			
Retarded	70	3,020 g (0.002) N = 25	3,300 g (0.002) N = 20
Controls	121	3,750 g N = 25	3,830 g N = 24
<i>Females</i>			
Retarded	67	2,900 g (0.002) N = 26	3,080 g (0.02) N = 20
Controls	124	3,360 g N = 26	3,440 g N = 25

N = number of children.

No birth weight of a retarded child was higher than that of the matched control. The probability such a correlation between IQ and birth weight is due to chance is infinitesimally small.

Among the children of normal to high intelligence, only two (3.9%) were of low birth weight. In contrast, 11 (21.6 per cent) of retarded children were underweight at birth. This difference is statistically significant at the 1 per cent level.

Bacola et al. did an anterospective study of low birth weight children, with groups of lower ($\leq 1,500$ g) [16] and higher ($> 1,500$ g) [17] birth weight groups. Forty children whose birth weight was more than 1,000 g but $\leq 1,501$ g were examined at an average age of 4.3 years [16]. Twenty-three per cent were mentally retarded; 15 per cent had neurological defects. Bacola et al. came to believe some of the twenty children considered to be normal had minimal brain damage which would be diagnosed at a later age. *Of the twelve children weighing no more than 1,250 g at birth, five (41.7%) were mentally retarded.* Mental retardation was three times higher in this group compared to the 28 weighing $> 1,250$ g at birth.

Sixty per cent of these children had respiratory difficulties as infants. There were 18 cases of respiratory distress syndrome (RDS), six of which were severe (see Chapter 5, p. 101). The incidence of RDS, especially severe RDS, was inversely proportional to birth weight, as reported by Bland et al. [42,43,440]. Severe RDS seemed to precede development of mental retardation. Bacola's data documenting the association between low birth weight and the development of RDS solidify the implications of the other studies (which show that a low cord protein level predisposes to RDS [42,43,161,257,440]) that prenatal malnutrition is an important factor in neonatal respiratory distress syndrome.

Infants experiencing early apnea of at least two minutes soon after birth showed more normal development than those who did not experience apnea. However, late apnea (at any time from a few hours after birth to two months of age) was significantly associated with neurological damage and mental retardation.

Since 80 per cent of deliveries were spontaneous, and sections were required in only 5 per cent of cases, matching typical random rates, the higher prevalence of RDS, mental retardation, and other neurological impairment cannot be attributed to labor or delivery. The authors noted that *in all nine instances of mental retardation, the children experienced severe RDS or late apnea and/or the mother had toxemia.* As previously stated, RDS [42,43,440,484] and toxemia [53-58,60,61,143,211,223,224,227,269,378,456-458,487,515,524,533,534,582,600] are consequences of malnutrition.

The authors also reviewed the results of medical examinations and IQ

tests of 48 children weighing $>1,500$ but $<2,500$ g at birth [17]. Four (8.25%) children had definite physical defects. This report confirms increasing birth weight and length of gestation as positive factors in a child's IQ, which increases dramatically as either (or both) factors improve. The average birth weight of children with an IQ under 75 was 397 grams less than the children with an IQ over 89. The average difference in length of gestation between the two groups was 39 days.

Knoblock and Pasamanick showed the developmental quotient (DQ) is also highly associated with birth weight [291]. In one study in which 90 per cent of infants had DQs between 90 and 120, a remarkable 80 per cent of infants with a DQ under 80 were underweight at birth.

There is some evidence that low birth weight infants born at term are more prone to develop neurological impairment than underweight, premature infants [19]. They are also more likely to have congenital anomalies [1]. Low birth weight, term infants characteristically have dry, loose skin and an abnormally small layer of subcutaneous fat [89]. These infants frequently have acidosis, polycythemia, and an increased hematocrit, all of which are likely related to chronic hypoxia.

Warkany et al. examined 27 low birth weight but term infants who were referred primarily because they had various mental or physical defects [552]. Only 22 survived. Of the survivors, one was deaf and four (18.2 per cent) had congenital heart disease. Six (27.3 per cent) were severely mentally retarded, nine others (40.9 per cent) were mentally deficient, and two (9.1 per cent) had borderline normal intelligence. That accounts for *all* 22 infants!

Many of the 27 mothers had nausea, developed toxemia, or had insufficient weight gain during pregnancy. All of these factors are nutritionally related.

Engleson et al. compared the health and development of 34 dysmature children (not defined by the authors) at birth with nineteen normal birth weight controls [163]. The controls, which were matched with the study group for sex, parity, and maternal age group, was selected randomly from a population in which both the mothers and the infants were free of diseases considered to affect the outcome of the study. The children were four or five years old when they were given extensive physical examinations. The examiner was not aware of which group any child was in. In general, the 53 children were of homogeneous socioeconomic status.

During the first six months of life, the dysmature infants gained weight at a more rapid pace than did controls, even though the dysmature infants remained smaller. The rapid weight gain was attributed to their increased nutritional requirements, suggesting strongly they had marked nutritional deficiencies. At age four or five, large weight deficits persisted. This is what

Drillien found to be true in Scotland [147-152].

Forty-four tests and measurements, most of them related to size, vision, reflexes, and neuromuscular control, were used to assess the health and development of these 53 children. The dysmature children scored significantly lower on this extensive medical analysis ($p < 0.002$).

Kerr Grieve did not summarize overall weight profiles in his unpublished compendium, but parts of the database apply directly to the question of birth weight sufficiency. Table 6-13 relates birth weights for primigravidas at Motherwell Maternity Hospital in 1972 and 1973 to births among Motherwell mothers delivering elsewhere.

Table 6-13
PRIMIGRAVID MEAN BIRTH WEIGHTS, MOTHERWELL
MATERNITY HOSPITAL DELIVERIES VS. MOTHERWELL
MOTHERS GIVING BIRTH ELSEWHERE (\pm S.D.)

<i>Place of delivery</i>	<i>Year</i>	<i>Number of births</i>	<i>Primigravid mean birthweight (g)</i>
Motherwell Maternity	1972	247	2873 \pm 420
	1973	241	2980 \pm 392
Delivery elsewhere (Motherwell mothers)	1972	48	3155 \pm 436
	1973	80	3198 \pm 422

Composite mean birth weights between hospitals, $p < 0.001$.

A greater disparity in birth weight is seen when Motherwell births are compared to those of Aberdeen (Table 6-14).

A significant concern in obstetrics during the middle of the 20th century,

Table 6-14
PRIMIGRAVID MEAN BIRTH WEIGHTS, MOTHERWELL
MATERNITY DELIVERIES VS. ABERDEEN (\pm S.D.)

<i>Place of delivery</i>	<i>Year</i>	<i>Number of births</i>	<i>Primigravid mean birthweight (g)</i>
Aberdeen	1968-70	1829	3393 \pm 415
Motherwell Maternity			
	1965	295	2944 \pm 438
	1966	260	2929 \pm 400
	1972	247	2873 \pm 420
	1973	241	2980 \pm 392
	1975	251	2940 \pm 407
	1976	217	2977 \pm 372

and one which has resurfaced in the 1990s for other reasons, was the advanced age of first pregnancy. This was defined then as any woman over the age of 30 years. The most extensive data summaries in Kerr Grieve's work relates to this group, as it was commonly believed they could not have fully healthy pregnancies and were especially prone to the onset of gestosis. Since adequate birth weight *per se* is the hallmark of successful pregnancy, given the relationship of birth weight to physiological and neurological development and maturation, one test of the appropriateness of the Motherwell Protocol is the outcome of pregnancy for *elderly* primigravidas, that is, women in their first pregnancy at ≥ 30 years. Table 6-15 compares a two-year sample of primigravidas, 1967-69, 456 *elderly* and 769 women between the ages of 20 and 29 years.

Table 6-15
BIRTH WEIGHTS: PRIMIGRAVIDAS ≥ 30 YEARS
COMPARED TO PRIMIGRAVIDAS 20-29 YEARS OLD

<i>Birth weight</i>	<i>Age ≥ 30 years</i> (456 cases)	<i>Age 20-29 years</i> (769 cases)
≤ 2500 g	63 (13.82%)	100 (13.00%)
2501-3000 g	188 (41.23%)	338 (43.95%)
3001-3200 g	104 (22.81%)	144 (18.73%)
3201-3400 g	50 (10.94%)	108 (14.04%)
> 3400 g	51 (11.18%)	79 (10.27%)

Percentages may not add to 100.00 due to rounding.

This internal comparison shows, at a glance, there was no difference in the birth weight profile for primigravidas irrespective of their age, 20-29 years, or 30 and above. Kerr Grieve examined many aspects of the obstetric course of elderly primigravidas, as noted in Chapters 4, 5, and 8. The gestational profiles in these two groups was the same (Table 6-16).

Essential hypertension was more frequent in the elderly primigravidas, 12.8 per cent versus 4.0 per cent for the 20-29-year old control group

Table 6-16
NEONATAL MATURITY BY GESTATIONAL AGE AT BIRTH

<i>Gestational age</i>	<i>Age ≥ 30 years</i> (456 cases)	<i>Age 20-29 years</i> (769 cases)
<36 weeks	18 (3.95%)	35 (4.55%)
36-37 weeks	34 (7.46%)	54 (7.02%)
38-40 weeks	390 (85.53%)	674 (87.66%)
> 40 weeks	11 (2.41%)	6 (0.78%)

Percentages may not add to 100.00 due to rounding.

described above. The relative prevalence of gestosis, by contrast, did not differ by much and was actually lower: 4.6 per cent against 6.5 per cent. Grieve noted often that this group of individuals was uncommonly motivated and the lower prevalence of gestosis in this group is consistent with that observation.

Ten elderly primigravidas were delivered by section during the period 1960-76, 2.19 per cent. Labor was surgically induced in the usual manner in 317 elderly primigravidas. There were just three sections for failed induction (0.946%) which is higher than the overall induction failure rate (Chapter 4, p. 62) of 0.3376 per cent, but the difference is not significant, since matrix equivalency would require only 0.04 of a section to be done in this group. This is obviously impossible! Ten sections were done for elderly primigravidas for a frequency of 2.19 per cent. The other seven were for specific indications other than failed surgical induction.

Finally, there was remarkably little perinatal mortality. Twelve perinatal deaths were recorded for the 456 primigravidous pregnancies in women 30 years old or beyond (2.63 per cent) but five were lethal anomalies, leaving a corrected perinatal death rate of 1.55 per cent (7/451 pregnancies).

The cumulative effect of these points from the Motherwell Protocol is to show the effects of dietary motivation toward good pregnancy outcomes does succeed even with a group of patients more generally considered to be at high risk due to their advanced age.

THE SPECIAL SUPPLEMENTAL FOOD PROGRAM FOR WOMEN, INFANTS, AND CHILDREN (WIC)

The Special Supplemental Food Program for Women, Infants, and Children (WIC) is a supplemental food program for low income pregnant, postpartum, and breast feeding women and both infants and preschool children.

The program is based on two *assumptions*. One is that inadequate nutritional practices and the health behavior of low income women and children make them especially vulnerable to adverse health outcomes. The other is that food interventions at critical periods of growth and development will prevent health problems and improve the health status of participants. The design of the program specified high quality protein, iron, calcium, vitamin A, and vitamin C as the nutrients likely to be consumed in less than adequate amounts by the poor, to be lacking in the diets of the targeted population.

A specific evaluation of the performance of WIC began in 1979 pursuant to a special congressional appropriation. The Food and Nutrition Service,

U.S. Department of Agriculture, sought applications and proposals for studies under the congressional mandate. The work was awarded to Research Triangle Institute of North Carolina. An advisory board was established and began to meet to review the progress of planning. Some time later, on the advice of the advisory committee, a new principal investigator, David Rush, M.D. (a person well known in medical nutritional circles at the time) was brought in. The final report was issued over five years after the start of the project; the soft cover report covers well over 1,000 pages in five volumes [465].

One major outcome measure was whether perinatal death rates were affected, but because death is rare, it was necessary to study very large numbers of births, many more births than could be gathered even in a relatively large study of current WIC recipients. The survey went back into earlier WIC records but, despite this special effort, the principal finding turned out to be that *perinatal death as an outcome measure was impracticable*.

The only alternative was "other significant disorders," more or less undefined, but birth weight was considered the likely substitute proxy for maternal health and pregnancy achievement.

A total of 6,563 pregnant women were recruited for study in 58 areas chosen randomly from the 48 contiguous states plus the District of Columbia. There were 5,205 first-time registrants for WIC benefits and 1,358 non-WIC individuals, also first-time registrants in either a health department or hospital prenatal clinic. There were 174 WIC program sites and 55 control units. The areas under study did not include much of the Great Plains, Memphis, Dallas-Fort Worth, Birmingham, Detroit, Columbus (Ohio), Charleston (South Carolina), Nashville, or Miami, all places with the sociomedical setting for probable adverse pregnancy outcomes.

The mean nutrient intake included 80.8 grams of protein per woman per day (Table 6-17), less than the Motherwell standard, and well under the recommendations of such workers as Tompkins and Wiehl, Dieckmann, Strauss, and others discussed in this book.

One should note the narrow difference for protein intake in the context of a distinction between statistically significant divergent group means (sets of numbers) and the biological importance of the difference. There were several specific findings within this context. *First*, the study found WIC supplemented pregnancies to last longer, a mean difference of 1.4 days. At this point a focal digression seems appropriate. The report is a large collection of data sheets carrying statistical operations, including multiple linear regressions, to incredible details, often down to six decimal places. All data from WIC is given as deviation from the mean of the controls. There are very few graphs, mainly comparative means or percentiles, and none of

Table 6-17

ADJUSTED MEAN DAILY NUTRIENT INTAKE IN LATE PREGNANCY FROM 24-HOUR DIETARY RECALLS, ADJUSTED FOR INTAKE AT STUDY ONSET* [465]

<i>Nutrients</i>	<i>WIC recipients</i>	<i>Controls</i>	<i>Difference</i>	(<i>p</i>)
Calories (kcal)	2016.1	1905.3	110.8	0.01
Protein (g)	80.8	75.5	5.3	0.01
Fat (g)	83.2	78.5	4.7	0.05
Carbohydrates (g)	240.8	228.3	12.5	0.05
Calcium (mg)	1003.7	871.0	132.7	0.001
Iron (mg)	17.2	14.1	3.1	0.001
Magnesium (mg)	269.3	243.8	25.5	0.001
Phosphorus (mg)	1382.8	1249.8	133.0	0.001
Vitamin A (IU)	6887.0	6109.3	777.7	n.s.
Thiamin (mg)	1.8	1.4	0.4	0.001
Riboflavin (mg)	2.3	2.0	0.3	0.001
Niacin (mg)	21.9	18.7	3.2	0.001
Vitamin B ₆ (mg)	1.9	1.6	0.3	0.001
Vitamin B ₁₂ (μg)	6.6	5.4	1.2	0.05
Vitamin C (mg)	144.1	111.7	32.4	0.001

*Total intake and intake from potential WIC foods at followup interview, controlled for initial intake, duration of gestation at both interviews, and maternal characteristics at registration into the study.

primary data in a comparative construct. Given the presumed wealth of information from an intense, detail-oriented study of this kind, this is a very large negative aspect of the report. Trying to find the data is also difficult; there is no index. Summary statements are linked to the relevant tables only rarely.

The operant question about the mean length of gestation is simply put: what biological meaning does 1.4 days convey, if any, since it represents 0.496 per cent of the modal length of human pregnancy. Careful analysis of data from the Collaborative Study indicates, by contrast, minimal rates for stillbirth and neonatal death rates over the time frame 39-43 weeks, within which no statistical distinction can be found [402]. There is no evidence to suggest any intrinsic meaning of a difference of 1.4 days.

The second finding was head circumferences for WIC infants was 0.18 to 0.21 cm greater than controls which were rated at a mean of 33.897 cm (the datum in the appended table was actually reported to six decimal places). Let us keep in mind how this measurement is performed: a tape measure is wrapped around the infant head along a certain assigned circumference, which may or may not be well matched. The summary asserts further that this difference is significant: $p < 0.01$.

Infant care, in the usual setting, does not allow for many repetitive measurements by which to assess intraobserver and interobserver

consistency. Indeed, use of this data was after the fact; it was taken from prior records. The WIC summary report appears to defend the point and the *p* value by a brief discussion on the relatively small medical literature on the subject. It is enough here to wonder, like the 1.4 days, what the biological significance of this might be. Since brain and skull conform to each other during fetal growth, this presumes an equally small difference in brain weight, data which is not available, of course, in the WIC setting. There is yet to be shown a correlation by which neonatal head circumference is a proxy for brain weight or function [130]. In addition, the presumed difference, we are told, was not from raw measurements but rather from means adjusted for sex and ethnicity.

Third, mean increased birth weight, 23 to 47 grams, was considered an important finding. Although there were reductions in preterm delivery, 23 per cent for whites, and 15 per cent for blacks, these factors are not effectively cross-correlated to show whether they were possibly causally linked.

Maternal weight gains (losses) and patterns of gain (loss) were so trivial, percentages notwithstanding (pregnancy weight in WIC registrants, i.e., mothers, was 80 grams more), no further comment will be made. Clearly, no distinction could be made, even accepting pregnancy weight as a useful predictor of outcome.

In discussion, the report does state that expansion of the plasma volume is strongly correlated with the health of the pregnancy and fetal growth, confirming Grieve [211-213], Rosso[459-462], and others [14,51,54-56,180]. WIC women had lower late pregnancy fat stores.

A critical point is the original outcome measure. The report is much confused internally on this. The following three paragraphs are quoted from pages V-1 and V-2 of the report summary (Volume I):

There were 3,192 singleton pregnancies of women recruited into the initial WIC sample. Among them were 31 fetal deaths, a rate of 9.71 (9.7) per thousand, and among controls there were 12 fetal deaths among 813 women, a rate of 14.76 (14.8) [per] thousand. This difference *was not statistically significant* (emphasis added).

The estimated effect derived from this analysis of WIC benefits on the fetal death rate . . . was a *statistically significant reduction* (emphasis added) of 2.3 per thousand. Since the mean fetal death rate over the 9 years for all women in the counties studied was 6.2 per thousand births, it represents a reduction of over one-third. [0.3709]

The estimated reduction in neonatal death rate associated with WIC benefits, *while not statistically significant*, (emphasis supplied) was of considerable magnitude. Receipt of WIC benefits was associated with a reduction of 2.3 deaths per

thousand live births, or a reduction of 22 per cent from the mean rate over the 9-year period of 10.6 per thousand live births. Thus, while the estimated reduction is large, this study, as large as it is, *was still not large enough to test for a difference of this magnitude* (emphasis added).

It is unclear how an observed rate of 9.7 per thousand is a reduction from a rate of 6.2 per thousand, despite the further observation of an even higher stillbirth rate for control pregnancies.

Interpretation of neonatal mortality seems a little more straightforward, at least as to the cautionary note provided above. A factor left out of these calculations is the impact of neonatal intensive care on immediate postnatal mortality [407,526], as discussed earlier in this chapter with reference to the work of Lubchenco [343].

One of the few broad scale tables with comparative information was Table IV-11, maternal age and reproductive history by WIC or control studies (page IV-53, Volume III). This showed borderline significance for the percentage of women with a prior birthweight ≤ 2500 g ($p=0.049$) but the significance was lost when subsets of this factor were considered. Control women were more likely to have had a prior induced abortion, 25.4 per cent.

Finally, little was done with the information on certain social habits of significance to pregnancy. At onset, WIC women smoked and drank less. Smoking actually increased during the course, but "not significantly more than controls," a comment not explained expressly. WIC did not seem to reduce alcohol consumption during pregnancy.

An effort was made several years later to report more fully and to explain and interpret the outcome as a supplement to the *American Journal of Clinical Nutrition* [466].

This is an equally interesting document. It starts off with some history of the program and a detailed explanation of the maximum monthly food allocation for *pregnant women and lactating mothers jointly, nonlactating puerperal women, infants and children*. It contains (pp. 394-411) a useful review of prior WIC studies. Overall, as a means to distill the massive WIC report into manageable form, it succeeds. The supplement also brings into sharp focus the failure of past studies as well as this one to track in an exhaustive fashion the original prime outcome measure, that is, preterm perinatal deaths which occurred early with the mother dropping out of WIC altogether. Instead, use of fetal mortality as proxy for both ran into collateral presumed factors, which the working parties could not break away from, such as the level of education.

The summary report was held up by the Reagan administration but was forced out and widely publicized by the media because the WIC program

was a popular political pressure point. Rush went before Congress in 1990 [467] to defend the report which in retrospect was neither as productive as its supporters were wont to claim nor as negative as its detractors were loud to assert.

The most singular achievement of WIC was improvement in the iron status of children up to the age of three years.

Viteri more recently provided some estimates of the scope of iron deficiency anemia [547]. First, it is the most prevalent nutritional disorder worldwide. Second, over 2 billion persons are iron deficient and 1.2 billion have iron deficiency anemia. Third, one-third of the developing world has iron deficiency. Fourth, 11 per cent of the industrialized world has iron deficiency, and fifth, 60 per cent of pregnant women are anemic world wide; in industrial countries this is 9-14 per cent [547].

Miller et al. examined the impact of the WIC program on the iron status of infants [375]. They found postnatal effects only; WIC had a benefit in that iron depletion and iron deficiency anemia became less common. The empiric data are of interest: Serum ferritin was significantly enhanced, $p < 0.005$. Hematocrit was not changed at six and nine months but became significant after nine months up to three years. After three years of age, iron status of children reverts slowly back to the more general situation, with all the consequences of iron deficiency as a *contributory* factor for other illnesses. Recent increases in the rate of overweight children in American schools prompted a review of WIC beneficiaries. NHANES III is a stratified multi-stage probability sample of the civilian, noninstitutionalized U.S. population ≥ 2 months old. Although, in general, the calories obtained from fats was higher for WIC children, no evidence could be adduced that the obesity observed was related to WIC [615].

The transitory conclusions of the WIC study respecting prior low birth weight infants and pregnancy terminations were noted above.

Roht et al. conducted an interview and mail survey in Japan on the association of multiple induced abortions with subsequent prematurity and spontaneous abortion [450]. Despite survey returns of a very high order (mail responses, 87.7 and personal interviews, 99.2%) no conclusion could be reached. There was a marginally higher risk for premature birth after pregnancy (8.97%) compared to premature birth without antecedent abortion is (7.71%) with $X^2 = 1.38551$, $p = 0.7089$.

Miller and Jekel found stronger data for association between unfavorable outcomes in successive pregnancies [374]. Spontaneous miscarriages in earlier pregnancies were linked with significant risks of later preterm births (< 37 weeks) (Table 6-18).

They defined high risk as one or more factors from a long list, which went

beyond the usual features of such inventories: high altitude, specific toxic exposure, multiple births, fetal infection, isoimmunization, inborn errors of metabolism, major malformations, gestosis, chronic hypertension, third trimester vaginal bleeding, elevated glucose tolerance test values, anemia (<10 g/dl), severe chronic disease, uterine malformations, major maternal drug therapy including corticosteroids, polyhydramnios or oligohydramnios, preterm spontaneous rupture of membranes, use of addictive drugs including alcohol and tobacco, malignant disease, low weight gain, pelvic tumors including leiomyomas, total lack of prenatal care, and pregnancy at the extremes of reproductive life. Low risk was the absence of all factors. This is not exactly a gradation of effect! Low birth weight was defined as <5th percentile on the Kansas City standard matrix.

Miller and Jekel concluded: (1) both outcome of prior pregnancy and risk factors in the index pregnancy had an influence of significance; (2) there was no interaction between these two factors, but they were additive; and (3) the current risk factors were more important.

Table 6-18
OUTCOME IN SUBSEQUENT PREGNANCIES
RELATED TO PRIOR PREGNANCY OUTCOME [374]

<i>Prior outcome</i>	<i>Risk level</i>	<i>Subsequent outcome</i>			<i>Total</i>
		<i>Normal</i>	<i>Preterm</i>	<i>IUGR/term</i>	
Miscarriage	High	27	14	19	60
	Low	20	2	4	26
Subset total*	47	16	23	86	
No miscarriage	High	111	41	31	183
	Low	103	4	7	114
Subset total*	214	45	38	297	
Grand total	261	61	61	383	

*Subsets recalculated: $\chi^2 = 7.12627$, d.f. = 2, p = 0.0283

When viewed as risk status for the index pregnancy, a fairly distinct pattern is obtained. Table 6-19 provides relative risks for three categories, birth weight, and state of maturity at two levels of gestational age: preterm and term.

An important critique of WIC is over the use of Recommended Daily Allowances (RDA) as a benchmark of performance. There is some cautionary language in the summary volume (Volume I, pages II-2 to II-6) but the comparison data, Table II-2, conveys a serious problem with the study as

Table 6-19
RISK STATUS OF INDEX PREGNANCIES [374]

Prior outcome	Risk status, index pregnancy		
	High [Row %] (Column %)	Low [Row %] (Column %)	Total
Term	188 [58.4%] (72.6%)	134 [41.6%] (95.0%)	322 (80.5%)
Preterm	55 [90.2%] (21.2%)	6 [09.8%] (04.3%)	61 (15.25%)
Low birth weight	16 [94.1%] (06.2%)	1 [05.9%] (00.7%)	17 (04.25%)
Total	259 [64.8%]	141 [35.2%]	400

Table $\chi^2 = 30.0717$, d.f. = 2, p≤0.0001

designed, analyzed, and reported. The table indicates that "only" 29.4 per cent of WIC women ate *less than the 77th percentile* of the RDA for protein while 31.8 per cent of controls ate below the 77th percentile. Since the RDA is an estimate of need, additional but unstated, possibly large numbers of these women clearly took in less than the RDA, namely those between the 78th and 100th percentiles.

Ryan et al. reported the effect of the WIC program on the nutrient intakes of infants in 1984 [468], from the Ross Nutrition Survey. They called attention to the critical point: RDAs are applicable to populations, not individuals. Some persons, taking less than the RDA for an ingredient, may not become deficient. RDAs are set high enough to "meet the nutritional needs of practically all *healthy* persons," but those for pregnancy and for premature infants are projections which do not account for their special needs or the requirements of intercurrent illness. Rather, one might say, this book and the research summarized here, are part of an effort to find out what the "RDAs" might be for pregnancy and underweight infants.

Metcoff et al. studied the effect of food supplements during pregnancy on subsequent birth weight [371]. They started with the assumption that 15-20 per cent of U.S. pregnancies resulted in infants significantly smaller *than they should be* given their sex, maternal size, race, and parity. They set out to test the hypothesis that pregnancies identified in midgestation as likely to have small or large babies could be affected favorably by the WIC program. They noted: ". . . except for change in body weight, objective data pertaining the effect of the WIC supplement on nutritional status are limited." Metcoff et al. speculated they would find an average gain in birth weight of 60 g; it was 91 g, about half of the Gambian experience, which had a wet season average of

186 g [427].

The debate over methodology and results continues. The many special procedural and technical problems were discussed recently in a symposium issue of the New York Academy of Science [4].

Buescher et al. examined the effect of the source of prenatal care on infant birth weight in a North Carolina county [74]. This was not a WIC study as such but had moderately effective WIC penetration into the pregnancy cohort of the area (Table 6-20).

Table 6-20
DEGREE OF PENETRANCE OF WIC INTO A
PREGNANCY COHORT AND LOW BIRTH WEIGHT [74]

	<i>Health Dept.</i>	<i>Private/ Medicaid</i>	<i>Private/ insurance</i>
Births	396	362	3279
<i>Program Penetration</i>			
Non-WIC	22.5%	55.5%	94.4%
WIC	77.5%	44.5%	5.6%
<2500 g	33 (8.3%)	70 (19.3%)	233 (7.1%)

This is an intriguing result. Low birth weight infants accounted for 8.3 per cent of the Health Department program with high penetrance of WIC; the Medicaid cohort with low penetrance had 19.3 per cent. Private patients, largely middle class with few WIC women, did the best, but little better than Health Department mothers with high WIC participation ($\chi^2 = 64.5453$, d.f. 2, $p < 0.00001$). As noted, the WIC assessment took several years. There was ample time during the efforts of the working parties to examine parallel literature and certainly more time was available during the preparation of the 1988 symposium in the *American Journal of Clinical Nutrition* [466]. This was not done.

During this interval, Nichols and Nichols published a review which was both thorough and provocative [400]. Among the critical comments and conclusions were:

(A) body stores of a nutrient result from accumulated intake minus metabolism and excretion:

BODY STORES = INTAKE - METABOLISM - EXCRETION

They assumed an efficient diffusion across the placenta but we know now placental transport is a mix of diffusion and active transport. Moreover, if most amino acids are resynthetized in the placenta, the concept of *diffusion*

as the principal mechanism is largely in error.

(B) Nutrient adequacy is the physiologic state in which supplementary nutrient intake is not associated with any increase in body stores as measured by nutrient concentration or by *nutrient mediated functions*. The latter is more important. In this context, Nichols and Nichols referenced the 1980 NRC recommendation for 21-2300 kcal per day, and,

(C) Large scale studies have shown an additional 10,000 kcal per gestation will increase birth weight and improve infant health, and an additional 20,000 kcal will do even better [309-313].

Table 6-17 indicates this threshold would obtain if pregnant WIC recipients kept on the program faithfully for 91 days. Although WIC recipients obtained an average of 110 kcal more per day than controls they were still only at 84 per cent of RDA. Controls were at 79.4 per cent of RDA. This is a mean value for the recombined racial subsets. Theoretically, this minimal cumulative energy intake was possible. Criteria for selection into the WIC study was for women to be less than 196 days pregnant at intake. The actual profile of WIC onset is not available anywhere in the summary statements of the original five part report [465]. Page IV-45, Volume III, has these statements:

The original study protocol also excluded women who were more than 6 months pregnant (196 days) at WIC enrollment or *entry into prenatal care* [emphasis supplied]. After 10 weeks of data collection, the study sample was smaller than expected and the proportion of women ineligible due to late duration of gestation at enrollment was larger than originally anticipated. Thus, it was decided partway through the study to broaden the study eligibility criteria to include both WIC and control women who were 7 or 8 months pregnant. Five hundred and seventeen such women, or 8 per cent of the final study sample, were ultimately recruited. (All analyses of birth outcomes in this report exclude these women [*parentheses in the original text*]).

Fifty-six per cent of WIC registrants had two or more nutrition education sessions, contrasted to 29 per cent of controls [466, p. 465]. There is no information on the intervals for the sessions; one gets the impression they were held ad hoc. Volume IV, pages V-139,140 contains the only relevant data on the point:

- (a) duration of gestation at initial interview, 125.1 ± 41.3 days and
- (b) duration of gestation at follow up interview, 236.0 ± 16.2 days
(means \pm standard deviation).

The difference between these means is 111 days, but the very large standard deviation for the initial gestational age clearly indicates many pregnancies had less than that number. The distribution of values is just not available. Equally critical is data in Table V-B-9 (p. V-78) which shows the

WIC caloric intake for white nonhispanics was actually less than the controls by 164 kcal per day. The only significant improvement in status by WIC was for blacks, 215.6 kcal per day over the controls who obtained 1851.4 kcal per day.

Seemingly, but not by any clear data provided, at least one subset of WIC recipients had reasonable caloric enhancement, but still at less than the RDA for pregnancy. The studies by Lechtig et al. [129,309-313], on which the 10,000 and 20,000 kcal supplements are based, actually started at a *lower* overall energy intake. These data are more paradoxical than contradictory. They point directly at the core of the problem: the energy entry level for pregnancy determines the amount of supplement requisite for successful enrichment of the pregnancy including the fetus and the upper limit of tolerance to high level supplementation. WIC failed to define these parameters and, accordingly, improvements in the outcome are marginal. The WIC supplement was too small to have measurable effects.

Naismith posited the fate of dietary protein is sensitive to the level of energy intake [393,394], which is the same conclusion reached by Kerr Grieve [211-213; see Chapter 4]. The possibility of hormonal roles in nutritional regulation, specifically aldosterone, has been raised [296]. It would be useful to know whether such studies involved salt restricted pregnancies.

Nichols and Nichols raise, indirectly, an important question [400]. All these lists of nutrients seem specific and are well considered, but if one goes back to the history of medical nutrition for the first half of the 20th century [447], a certain point becomes clear: the discovery, identification, and synthesis of B vitamins, so critical for metabolism, has been an episodic enterprise, one most likely still incomplete. Thus, the question is: what nutrient(s) yet to be identified are necessary, if any, for the most efficient growth and maturation of the human fetus?

GAMBIAN STUDIES

In a series of important papers over a decade, Prentice et al. [425,427-430] explored the biology of supplementation in a population functioning at caloric intake quite low by American experience. The first paper came out in 1983 [427]. Women were studied in a rural area of Gambia, one of the smallest countries in Africa, on the westernmost coast of the continent. There is a unique geography to Gambia. It is riverine, essentially a narrow strip of a country along the Gambia River, with an extremely well defined wet season, June through October. August, the month with the heaviest rainfall,

may see as much as 50 cm of rain (19.7 inches). The river often floods, bringing new loam, replenishing the water table. Further west, near the capital, Banjul, agricultural lands are sometimes flooded by salt water from the Atlantic Ocean, which is often leached out during the rainy season. There is low average life expectancy. An average of 1480 kcal were eaten during the dry season and a minimum of 1300 kcal in the wet season. These women showed positive energy balance in the dry season but not in the wet months of the annual cycle. They studied 93 gestations (51 in the wet season, and 42 in dry season). Supplements in the wet season yielded an average increase in birth weight of 186 grams. The difference between seasons, despite the small samples, was significant ($p<0.01$). The birth weights before and after supplements by season are shown in Table 6-21.

Table 6-21
BIRTH WEIGHT PERCENTAGE PROFILE,
BY SEASON OF SUPPLEMENTS, GAMBIA [427]

	<i>Dry season</i> (supplement)		<i>Wet season</i> (supplement)		<i>Ratio</i>	
	<i>Pre-</i>	<i>Post-</i>	<i>Pre-</i>	<i>Post-</i>	<i>dry:wet season</i> <i>Pre-</i>	<i>Post-</i>
>3500 g	5.4	8.0	2.2	11.6	2.45	0.69
3001-3500	40.4	42.0	25.8	37.2	1.55	1.13
2501-3000	42.5	42.0	43.8	46.5	0.97	0.94
<2500	11.7	8.0	28.2	4.7	0.41	1.70
χ^2	n.s		$p<0.01$			

They concluded the overall state of energy balance is the key to the outcome; dry season activity did not require caloric supplementation but the wet season did and their metabolism was responsive to supplementation. The seasonal variation was 180 kcal per day. The right hand double column, ratios of distribution for dry season over wet season (data calculated here, not reported by Prentice et al.) shows the favored dry season presupplement in a progressive, highly favorable light. By contrast, birth weight allocations post supplement have ratios which are not linear but which tend to favor lower birth weights, indicating some effect in weight distribution beyond that identified clearly by mean values.

Prentice et al. continued to expand their study and reported on 197 rural Gambian women in 1987 [428]. Supplementation continued to be ineffective during the dry season but was very effective during the wet season: unadjusted, a 225 ± 56 gram gain; adjusted for infant sex, parity, and season a 231 ± 65 gram gain, both significant at $p<0.001$. Prentice correctly criticized various low yield studies because their target groups were women

with physical indices of low maternal nutritional status or history of previous low birth weight infant(s). Such outcomes are exactly what one should expect under those circumstances, namely, little evidence for positive effects of diet supplements. The WIC analysis authored by Rush fits into this category.

Prentice et al. related their work to other studies in 1991[429]. Their review of available evidence indicated a number of important points for consideration:

1. Supplementation in late pregnancy (second half) has significant benefits for women at risk due to otherwise (read: "home") inadequate diet.
2. Statistical projections predict the increase in birth weight should be accompanied by a significant decrease in neonatal or perinatal mortality.
3. Supplementation during lactation is unlikely to raise either output or quality of the milk, except perhaps in the most extreme cases of maternal malnourishment.
4. An unstated aspect of the latter point is the question whether intra-lactational supplement will benefit the subsequent pregnancy(ies).

Prentice et al. went on to chide the Rush, Susser, and Stein school of pregnancy nutritional thought over their expressed pessimism for saying (and writing) that data accretion for pregnancy nutrition has such severe problems it is virtually impossible to interpret the data and draw conclusions.

Prentice et al. remarked: "We take a more pragmatic view and believe that the issue of such importance that we must make the best of the data available."

This is exactly the point. When expressed analytically, the question becomes: are the defects or faults of a study sufficient to overcome the positive information obtained?

This author's position is to agree fully with Prentice and his many associates: there is a lot of very good information in many studies, data which answers much of what needs to be known for effective planning of nutritional intakes for pregnant women. Moreover, their many papers show exactly how the basic biology of human pregnancy nutrition is *only understood* in the context of the societal and geographical milieu in which the pregnancy takes place. If you want to study the effect of nutritional supplements against the basal requirements of human pregnancy, do so in a place where the baseline is really bad: Gambia, not American city and county health departments. This is not an exculpation of what has been achieved in the United States, quite the contrary. What we are trying to do in the United States is optimize from a platform of modest sufficiency for most. There are truly nutritionally deprived women in the United States, but their problems are focal or linked qualitative deficits, not global protein and calorie inadequacies. Contrast the

marginal results from WIC, as explored by Rush, with the clear improvement in Gambia starting from and ending at much lower levels of energy intake!

Finally, Prentice and associates studied the fundamental energy physiology of the pregnant state in Gambia [425,430]. Changes in basal metabolic rate (BMR) relative to nonpregnant, nonlactating baselines, were arbitrarily divided into "energy profligate" and "energy sparing" groups. The changes in the former were positive with rare exceptions and the latter were negative in the main. Energy rose in late pregnancy even for some whose midpregnancy levels fell. Increases in BMR by 10-30 per cent were common.

Energy needs were expressed in MJ (megajoules) and kJ (kilojoules). Per diem accumulative findings ranged from -220 kJ/day to +3100 kJ/day! The energy balance for pregnancy requires 1492 kJ/day or 418 MJ per pregnancy. This is a high cost. They noted further that some have pegged the need rather lower, based on food intake diaries (e.g., U.K. Department of Health, 1991 [585]). Prentice et al. studied several women longitudinally and found wide discrepancies between total energy expenditure (TEE), BMR, and known energy intake. Unreliability of food intake records in even apparent good subjects is well known as shown by others [40,41,201,202,335,430,475], and was seen in their own work [425]. Poppitt et al., in a 1994 paper from the Prentice group, found marginally nourished pregnant women conserve energy by lowering their basal metabolic rate and gaining little fat tissue [425]. They reviewed ten data sets with longitudinal measures of the energy costs of pregnancy, a total of 360 pregnant women. When birth weight (kg) is graphed against the maternal weight gain (kg), a linear relation is obtained. The linear regression equation which results is:

$$\text{Birth weight (kg)} = (0.121211 \times \text{Weight gain in kg}) + 2.01443.$$

Simplified, this is: $BW(\text{kg}) = (0.12 \times \text{Weight gain in kg}) + 2$. A woman gaining 10 kg would have, on average, an infant weighing:

$$\begin{aligned} BW &= (0.12 \times 10) + 2, \\ BW &= 3.2 \text{ kg} \end{aligned}$$

Gambia is surrounded by Senegal except for a narrow Atlantic coast. Another challenge to the concept of fetal growth by the mass action of food intake comes from neighboring Senegal [63]. Briend's brief observational paper does not provide extensive primary data. The value of the report is the observation there was a seasonal variation despite birth weights less than expected given the size of the women. The lowest birth weights occurred between October and February.

Senegal has about ten times the population of Gambia, is 30 per cent urban (compared to 10 per cent), with half the population density of Gambia. These demographic-environmental factors play a role in food supply and nutrition. The study was performed in metropolitan Dakar which has a wet season from July through September, when the same women would be entering or going through their third trimesters of pregnancy [63]. The wet season around Dakar yields about half the rain fall seen in Gambia, with less temperature variation.

On this information, Senegal has a muted seasonal fluctuation for food supply relative to Gambia, and the pregnancy result is also muted but in the same direction. Briend made comparisons to pregnancy outcomes from Aberdeen from the 1960s, not strictly as controls which they could not be, but for an indication of progression of birth weight against maternal weight gain.

Chapter 7

THE CORRELATION OF PRENATAL AND PARANATAL COMPLICATIONS WITH NEUROLOGICAL DISORDERS

FOR MORE THAN A HUNDRED AND THIRTY YEARS, associations between cerebral palsy (CP) and "abnormal parturition, difficult labors, premature birth, and asphyxia neonatorum" have been recognized [334]. Sigmund Freud challenged the remarkable, commonly held view of 1897, that the *fetal* cerebral palsy caused *maternal* complications and *gestational* prematurity [185]. Freud came to believe that prematurity, dystocia, and asphyxia, when accompanying the birth of a child with cerebral palsy, were caused by the same developmental (usually environmental), prenatal, and paranatal factors causing the cerebral palsy. In the late 1940s, Lilienfeld and Parkhurst undertook extensive retrospective studies of cerebral palsy in children born in upstate New York. They sought to find out whether prematurity and maternal complications caused cerebral palsy, whether cerebral palsy caused premature labor and other maternal complications, or if they were primarily unassociated dependent variables due to other factors [329]. Unfortunately, they did not retrospectively assess the nutritional status of mothers of the children with cerebral palsy.

The authors examined the prenatal records of all singleton CP children born between 1940 and 1947 surviving the neonatal period. Medical records of 561 such children with accessible records were analyzed. Relatively few instances of cerebral palsy were found for births after 1945 because, at the time of the study, these children were of preschool age; some may have had undiagnosed cerebral palsy. The authors estimated their 561 cases represented approximately 75 percent of all cases of cerebral palsy, since

they believed very mild cases (often undiagnosed) and the most severe cases (often neonatal deaths) together constituted about 25 per cent of infants with CP. Given their contribution to low birth weight and gestational prematurity, the higher incidence of multiple births (3.4%) in cerebral palsied children found by Lilienfeld and Parkhurst confirms the expectation.

The contribution of twinning and multiple pregnancies to the pathogenesis of developmental neurological abnormality has been undervalued and little studied. Many of the useful reports were examined as functions of low birth weight in Chapter 6. Part of the problem is the relative infrequency of multiple births. Baldwin, in arguably the best modern text on the pathology of multiple pregnancy [21], summarized the rather wide variation in the frequency of twins (her page 21). The highest frequency commented upon by Baldwin was 1:33 among the Ibo of eastern Nigeria and the lowest was 1:178 in Japan. Strong and Corney [516], writing more specifically on twin placentas (their page 26), summarized the standard rule propounded by Hellin [238] in 1895:

If the frequency of twins = n , then the frequency of triplets = n^2 , and the frequency of quadruplets = n^3

A fairly standard range of occurrence discussed over the years has been for $n = 80$. Hellin used $n = 88$, or 11.4 twin sets per 1000 births. Assuming that both twins survive, the actual number in the population would be 1:44. The 16th edition of *Williams Obstetrics* noted different frequencies of the major subtypes of twinning, features of potential significance in divining aspects of pathogenesis [432, p. 639]. They set the frequency of monozygotic twinning at 1:250, with the remainder dizygotic. This distinction makes little difference in overall considerations of statistics but may well have more importance biologically. Neither Churchill [102,103] nor Drillien [147-152] made the distinction which, of course, would have involved just a few of their study cases.

Taking Hellin's Rule and a middle of the road American estimate, 1:80, triplets would account for only 1:6400 births. Nevertheless, higher representation of triplets or higher amongst children with cerebral palsy or other paranatal neurological conditions would constitute strong evidence for pathogenesis. *Williams Obstetrics* makes the further point that modern therapies for infertility materially change the singleton: multiple birth ratios [432, pp. 641-642]. Multiple fetuses account for as many as 20-40 per cent of pregnancies after gonadotropin therapy, and the total count of conceptuses exceeds the natural process (to 9 and 11 per *Williams Obstetrics*). Clomiphene, which has a different mode of action, is less profligate, but twins accounted for 6.9 per cent, triplets 0.5 per cent, and quadruplets, 0.3 per cent. The expected ratios, expressed in the same fashion, are: twins, 1.25 per cent;

triplets, 0.0156 per cent; and quadruplets, 0.00019 per cent!

Neither of the monographs from the Collaborative Study included data on twin effects, beyond a brief note in passing [229,402] on possible enhanced risk for congenital heart disease. Baldwin cited Myrianthopoulos [390] on a racial difference in the United States, 1:100 for whites, and 1:79 for blacks, on data culled from the Collaborative Study.

Fifty years ago, Lilienfeld and Parkhurst [329] observed a high correlation between cerebral palsy and both low birth weight and complications of pregnancy. Although they did not control for socioeconomic status, age, parity, month, or season of birth, and other factors, their data showed the association of low birth weight with the development of cerebral palsy is independent of other complications during pregnancy and parturition. They also discovered when one or more complications of pregnancy accompany the birth of underweight infants, there is an increased chance of both cerebral palsy and early childhood mortality.

The birth weights of and maternal complications behind 517 infants with cerebral palsy were compared to the same factors in 377,764 infants born during 1942-45 which survived the neonatal period without CP. Low birth weight frequency in children with cerebral palsy was 22.2 per cent in comparison to 4.8 per cent among the controls ($p<0.0001$). The relative difference in complications of pregnancy was nearly as dramatic as that for low birth weight ($p<0.001$). Nearly 38 per cent of CP children were born to mothers with complications; the prevalence of complications of pregnancy among the neonatal survivors was 19 per cent.

The data imply that low birth weight and complications are interdependent factors in the development of cerebral palsy. Their association with one another reflects a common etiology, at least in part. Children with cerebral palsy accounted for 32 per cent fewer of the low birth weight infants when their mothers had complications. In contrast, the neonatal survivors had 50 percent *more* low birth weight children among mothers with complications. For women without obstetric complications, the low birth weight rate was six times higher for cerebral palsied children than among the 1942-45 neonatal survivors. For women with complications during pregnancy, the low birth weight prevalence was less than three times higher for mothers of children with CP, compared to offspring of control mothers. The authors attributed the difference in *complication dependent* low birth weight to a high neonatal or perinatal mortality rate for low birth weight infants whose mothers had complications. They reported 17,820 perinatal deaths in 395,584 births, or 4.5 per cent, not a high rate for 1942-1945. There is another way to look at these particular points in their report [329]. Low birth weight with no complications of pregnancy has a certain risk for cerebral

palsy, but when low birth weight occurs with complications, both will contribute to lesion formation, synergistically, *reducing the necessity for contributory injury* from low birth weight alone. In addition, since the study design using neonatal survivors as controls eliminated stillbirths and neonatal deaths, it excluded many infants of low birth weight whose mothers had complications, and exaggerated the comparison. No data was given by which to assess possible effects of this factor. Nevertheless, the database was extremely large and the special study group with cerebral palsy also contained survivors, so the overall effect of the differences is likely to remain significant and biologically important.

Taking the long view, the patterns and associations establish the validity of pathogenetic relationships between low birth weight and pregnancy complications with cerebral palsy as one neonatal outcome. This was the conclusion mentioned in the first edition of this book, but recalculation of the original data actually makes the case more strongly. Table 7-1 outlines the prevalence of CP by birth weight and whether maternal complications occurred. The percentage of infants by weight classes which have cerebral palsy varies by weight class. There is a steady decline in relative prevalence of observed cases as birth weight rises, reaching 1.87 per cent with birth weights $\geq 2,500$ grams (Table 7-1).

Table 7-1
PREVALENCE AS PERCENTAGE OF INFANTS PER BIRTH WEIGHT
CLASS AND PRESENCE OR ABSENCE OF LATE PREGNANCY
MATERNAL COMPLICATIONS [329]

<i>Birth weight</i>	<i>Maternal complications</i>	<i>No maternal complications</i>
<1,500 g	18.99%	6.92%
1500-1999 g	14.11	5.25
2000-2249 g	5.60	1.595
2250-2499 g	4.30	0.886
≥ 2500 g	1.87	0.268

Table 7-2 compares the number of cases of CP observed per birth weight class against the expected number; the table also records whether maternal complications were present. The expected values are recalculated from the original paper [122]. There were 505 cases of CP with known birth weight from mothers with reported complications and 318 with known birth weight from mothers with no reported late pregnancy complications [329]. Lilienfeld and Parkhurst originally calculated the figures for expected cases from raw data in the upper part of their table 6 but rounded off to whole

integers. Recalculation (Table 7-2) shows the actual ratio without rounding (in italics) and this generates an even more compelling pattern (Table 7-3).

Table 7-2

505 CASES OF CEREBRAL PALSY BY BIRTH WEIGHT AND OBSTETRIC COMPLICATIONS CONTRASTED TO 318 CASES FROM UNCOMPLICATED PREGNANCIES (EXPECTED NUMBER OF CASES PER WEIGHT GROUP OR STATUS IN ITALICS) [329]*

<i>Birth weight</i>	<i>Mothers with complications</i>	<i>Cerebral palsy</i>	<i>Mothers without complications</i>	<i>Cerebral palsy</i>	<i>Total mothers</i>
<1500 g	79	15 (0.35)	159	11 (0.70)	238
1500-1999 g	326	46 (1.43)	629	33 (2.76)	955
2000-2249 g	375	21 (1.64)	1,003	16 (4.39)	138
2250-2499 g	697	30 (3.05)	2,258	20 (9.89)	2,955
≥2500 g	20,994	393 (91.9)	88,757	238 (388.8)	109,751

*12 cases with unknown birth weight eliminated from calculations.

The recalculated ratios of observed to expected are dramatic for both clinical categories, complicated and uncomplicated (Table 7-3).

There is a steady rise in the number of expected cases because there is a steady rise in the number of infants per birth weight range, in part.

Of interest, the frequency of cerebral palsy in their off-spring was higher for women either younger than 20 or 30 or more years old than for mothers in the decade 21-30 years. An association between birth order and cerebral palsy was slightly stronger compared to when age was considered alone. Neither trend, however, attained statistical significance. Equally, if not more interesting, primigravidas and women in their fourth or higher pregnancies were the most likely to have CP children. A similar birth order distribution

Table 7-3

RECALCULATED RATIOS OF OBSERVED TO EXPECTED CASES OF CEREBRAL PALSY BY BIRTH WEIGHT AND PRESENCE OR ABSENCE OF MATERNAL COMPLICATIONS [329]

<i>Birth weight</i>	<i>Observed:expected ratio</i>	
	<i>Maternal complications</i>	<i>No maternal complications</i>
<1,500 g	42.89	15.71
1500-1999 g	32.17	11.96
2000-2249 g	12.80	3.64
2250-2499 g	9.84	2.02
≥2500 g	4.28	0.61

has been found among epileptics [62]. The association of low birth weight with age and parity was similar to that of cerebral palsy with age and parity.

Lilienfeld and Parkhurst concluded the relationship between cerebral palsy and age and parity merely reflected the more basic association of cerebral palsy with low birth weight and, therefore, age and parity are not causally related to cerebral palsy.

Yerushalmy et al. found mothers with a history of previous infant loss to have a subsequent risk of infant loss twice that of mothers with no previous infant loss [576]. Among mothers with CP children, the ratio of observed previous infant loss to an expected number, was 1.35. The expectation was calculated from the total birth population of 1942. Hence, younger siblings of CP children experienced 35 per cent more deaths than expected on general demographic terms.

Operative procedures for delivery were not a factor in the development of cerebral palsy. Thus, evidenced by an independent or interdependent association with low birth weight and pregnancy complications, cerebral palsy occurs during the prenatal period; there is an absence of association with other factors.

Thirty-seven per cent of mothers of the cerebral palsy population had one or more complications during pregnancy, compared to 21 per cent of mothers of the 1942-45 neonatal survivors.

The possibility of underreporting of complications was considered by Lilienfeld and Parkhurst [122]. This would be a minor confounding factor because approximately 90 per cent of birth certificates did have enough information concerning complications.

Premature separation of the placenta and toxemia were very frequent among the mothers of CP children and among the 1942-45 mothers delivering stillbirths or infants dying neonatally [329]. Table 7-4 reveals risks of pregnancy complications, abruptio placentae, and toxemia for these two groups.

Figure 7-1 depicts ratios of the observed versus the expected but calculated prevalences of various prenatal and paranatal maternal complications, using the 1942-45 neonatal survivors as baseline. As the bar graph makes clear, many complications were especially commonplace in the stillbirths and neonatal deaths. Lilienfeld and Parkhurst declared:

There appears to exist a relationship between stillbirths, neonatal deaths, and cerebral palsy. The pattern of factors, such as complications of pregnancy, prematurity, etc., which influence infant loss seems to behave in a similar manner with regard to cerebral palsy (p. 278) – It appears that the preventive aspect of a cerebral palsy program should be placed within the general scope

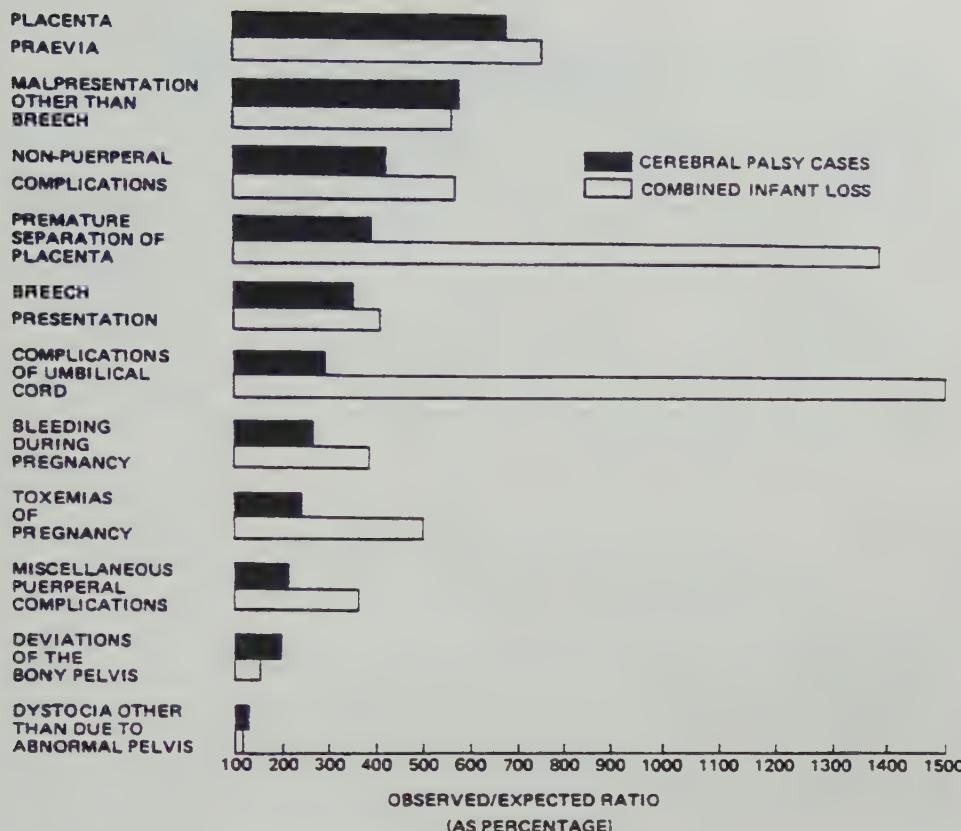


Figure 7-1. Ratio of observed to expected cerebral palsy cases, combining infant loss and complications of pregnancy. (Courtesy of A.M. Lilienfield and A. Parkhurst: A study of the association of factors of pregnancy and parturition with the development of cerebral palsy. *Amer J Hyg.* 53:262-282, 1951.)

of a maternal health program (p. 278) – The association of several factors of pregnancy and parturition with the development of cerebral palsy was of a pattern similar to that prevailing in combined infant loss. This relationship suggests . . . the existence of a “continuum of reproductive wastage,” with a lethal component consisting of abortion, stillbirths, and neonatal deaths, and a sublethal component consisting of cerebral palsy and perhaps other related conditions. (p. 280) [329]

It is appropriate to mention that the rate of cerebral palsy in the United States is three times Norway's [3]. Eastman examined the relation between cerebral palsy and race, age, and parity. No association was found with or among these factors [153], an observation which enhances the environmental hypothesis.

Table 7-4
RELATIVE RISK FOR PREGNANCY COMPLICATIONS
AMONG MOTHERS OF CHILDREN WITH CEREBRAL PALSY [329]

<i>Status</i>	<i>Years of study</i>	<i>Complications of pregnancy</i>	<i>Abruption</i>	<i>Toxemia</i>
Cerebral Palsy (N = 517)	1940-47	37.8% (p<0.0001)	1.0% (p=0.01)	3.3% (p=0.02)
Survivors (N = 377,764)	1942-45	20.9%	0.3%	1.8%
Perinatal Deaths* (N = 17,820)	1942-45 (p<0.0001)	62.4% (p<0.0001)	10.8% (p<0.0001)	10.3%

*Stillbirths and neonatal deaths combined.

FACTORS ASSOCIATED WITH A CONTINUUM OF REPRODUCTIVE CASUALTY

Breakthroughs in the field of developmental disabilities have been made by Pasamanick, Knobloch, and Lilienfeld, who contributed extensive research on secondary causes of reproductive casualty for nearly thirty years. They developed and advanced the theory of a "continuum of reproductive casualty" [277,414,415] to designate: "Sequelae of harmful events during pregnancy and parturition resulting in damage to the fetal or newborn infant, and primarily localized to the central nervous system [414]." They were meticulous and thorough in analysis which effort fully confirmed the hypothesis. Since complications of pregnancy and low birth weight are associated with perinatal death, a significant number of neonatal survivors underweight at birth and/or whose mothers had complications were afflicted with permanent neurological damage [414]. Although these concepts were introduced a hundred years ago [24], Pasamanick et al. were among the first, and certainly the most energetic of their time, to grasp the implications in terms of prevention. Their extensive research, which directly linked infant and child health to maternal health, showed there is a significant association between prenatal and paranatal complications and a gradient of injury [415], including, in probable order of significance, from a developmental time vector view, spontaneous abortion, perinatal death, cerebral palsy, mental retardation, and behavioral disorders [277].

The concept of this continuum was supported by Benton [34]. The connection is secure; lacking is how quantitative the matter is given the cumulative knowledge of the past century. One objective of this book is to

bring this into better focus.

A major review of prospective and retrospective studies which linked mental deficiency to prenatal and postnatal factors documented the minor extent to which chromosomal abnormalities and genetically-transmitted metabolic disturbances actually contribute to mental retardation and other developmental disabilities [292]. In their review of 155 publications, Knobloch and Pasamanick showed that such epigenetic disabilities are basically preventable.

Tables 7-5 and 7-6, which summarize several well-controlled retrospective studies, reveals the high association between maternal complications, low birth weight, and neonatal abnormalities, and various neuropsychiatric disorders [414] and epilepsy [330]. The cerebral palsy study [329], which is included in this table, was reviewed at the start of this chapter. Studies on three groups of children whose predominant disorder was either autism, mental deficiency, or reading disorders will be discussed in detail later. Data from these studies are provided in Tables 7-5 and 7-6.

Knobloch and Pasamanick, in a prospective study, analyzed the relationship between behavior and emotional stability and birth weight [293]. In examinations taken at age three years, the higher birth weight children were given superior ratings respecting organization of behavior, discrimination, judgement, emotional stability, attention span, perseverance, irritability, restlessness, and quality of integration. The differences in examination scores between higher and lower birth weight children were significant statistically. They concluded,

The findings point to the overwhelming importance of the factors of prenatal maternal health, preschool stimulation, and later educational effort which are the major foci in the antipoverty programs for children today. These programs should be geared to the elimination and modification of such results of poverty and deprivation as malnutrition, infection, and other forms of stress, prenatally in the mother, and postnatally in the child. [294]

After years of follow up, Pasamanick and Knobloch observed that infants underweight at birth or born to mothers with complications during pregnancy, or both, are afflicted frequently with minimal brain damage not diagnosed initially [414]. Extensive research supports the contention that minimal brain damage usually starts during the prenatal period. In one study, strabismus, a complex of many focal functional abnormalities, is likely a form of minimal brain damage and was found to be significantly correlated with complications of pregnancy and low birth weight [413].

A study by Pasamanick of children with behavioral disorders showed that hyperactivity, which some health care workers consider to be subclinical epilepsy, was highly associated with maternal complications and low birth

Table 7-5
ASSOCIATION OF NEUROPSYCHIATRIC DISORDERS
WITH PRENATAL AND PARANATAL COMPLICATIONS [414]

Disorder	Number of children	Low birth weight		Level of significance
		Study group	Controls	
Autism	50	21.0%	12.0%	N.S.
Behavioral disorders	840	8.8%	2.8%	<0.0001
Cerebral palsy	561	22.0%	5.0%	<0.0001
Epilepsy	396	13.6%	6.4%	N.S.*
Hearing disorders	124	16.1%	7.3%	0.05
Mental deficiency	639	17.1%	8.7%	0.0005
Reading disorders	205	11.5%	4.6%	0.05
Strabismus	398	13.6%	7.8%	0.01

*There was a significant difference for white infants but not for either blacks or the whole group with epilepsy [330].

weight [414]; this was confirmed by another independent study [330,449]. One physician estimated that more than 5,000,000 children in the United States have hyperkinesis and related learning disabilities, signifying a five-fold increase since the early 1950s [168]. This dramatic rise in the prevalence of hyperactivity in the United States occurred concurrently with an increase in the use of diet suppressant and salt depleting drugs, the latter often with restrictive dietary regimens during pregnancy [53,60]. This work was prescient toward the very modern concern on environmental toxins across a

Table 7-6
ASSOCIATION OF NEUROPSYCHIATRIC DISORDERS
WITH PRENATAL AND PARANATAL COMPLICATIONS [414]

Disorder	Number of children	Pregnancy complications		Level of significance
		Study group	Controls	
Autism	50	51.0%	17.0%	0.0005
Behavioral disorders	840	40.9%	31.7%	0.0005
Cerebral palsy	561	38.0%	21.0%	<0.0001
Epilepsy	396	34.8%	26.4%	0.05
Hearing disorders	124	24.0%	11.5%	0.01
Mental deficiency	639	43.8%	36.2%	0.05
Reading disorders	205	37.6%	21.5%	0.0005
Strabismus	398	22.9%	16.1%	0.02

broad spectrum of health issues.

Study of fifty autistic children showed that 21 per cent were of low birth weight and 51 per cent of the mothers had at least one complication during pregnancy (Tables 7-5 & 7-6) [414].

Significantly, in virtually all of their studies, Pasamanick, Lilienfeld, Knobloch, Parkhurst, and Kawi found no major contributory causal factor in dystocia or operative delivery (forceps, section, internal podalic version) [414]. This research refutes the myth that delivery means are major pathogenetic factors in adverse infant outcome (an attitude common in the 1960s to mid-1980s among physicians and still acted upon by attorneys at the end of the 20th century). There is little evidence, if any, to link mode or means of delivery to long-term poor health or the presence or extent of neurological damage. Instead, it has become clear that most factors which affect the course of pregnancy also influence the outcome.

Pasamanick and Lilienfeld tested and later rejected the hypothesis that epilepsy is basically genetic, a theory which, unfortunately, was still accepted in the 1960s [340,414]. They showed epilepsy to be highly associated with complications of pregnancy. Epileptic children were not overrepresented from mothers with complications. The conclusion was that epilepsy was caused by prenatal and paranatal environmental factors (Table 7-7).

Nelson and Ellenberg demonstrated maternal seizures during pregnancy were a factor in subsequent infantile and childhood neurological abnormalities [396]. One possible mechanism comes from the recent demonstration that maternal complex partial seizures can affect fetal rates [395]. An experimental model in the rat confirmed cerebral tissue damage from induced maternal seizures [222], but an assertion of preventive value from magnesium sulfate does not bear close scrutiny.

Table 7-7
LOW BIRTH WEIGHT, MATERNAL COMPLICATIONS,
AND THE PREVALENCE OF EPILEPSY [330]

Patient status	Total births	Maternal complications			
		Complications		No complications	
		Births	Low birth weight	Births	Low birth weight
<i>White</i>					
Epilepsy	263	71	18 (25.4%)	192	16 (8.3%)
Controls	264	47	3 (6.4%)	217	7 (3.2%)
<i>Nonwhite</i>					
Epilepsy	122	56	11 (19.6%)	66	8 (12.1%)
Controls	121	53	9 (17.0%)	68	6 (8.8%)

All four principal cells of Table 7-7 reflect higher cross affinity between maternal complications, low birth weight, and epilepsy but the relative ratios

Table 7-8
RATIO OF CROSS AFFINITY, EPILEPSY TO
CONTROLS, IN LOW BIRTH WEIGHT [330]

<i>Maternal complications</i>	
White	3.969
Nonwhite	1.153
<i>No maternal complications</i>	
White	2.594
Nonwhite	1.375

differ widely (Table 7-8).

These ratios summarize an additional feature across the large body of work by Pasamanick and his many associates over the years: the effect of complications, including low birth weight *per se*, has less additive effect in blacks or nonwhites (as defined by each of the studies) than in pregnant whites. It is not a matter of small sample sizes. Sample size might be considered a factor due to the share of the American population which is black or nonwhite, 9.9 per cent in 1950¹, a time point in the middle of these studies, but Pasamanick and others expanded efforts in every instance to obtain samples of effective size. Table 7-7, for example, has 527 whites and 243 nonwhites. By due diligence, population ratios are not a factor in comparative analysis of pregnancy and neonatal status.

Table 7-9
LOW BIRTH WEIGHT, MATERNAL COMPLICATIONS,
AND THE PREVALENCE OF MENTAL RETARDATION [415]

Patient status	Total births	<i>Maternal complications</i>			
		<i>Complications</i>		<i>No complications</i>	
		<i>Births</i>	<i>Low birth weight</i>	<i>Births</i>	<i>Low birth weight</i>
<i>White</i>					
Retarded	381	136	35 (25.7%)	245	27 (11.0%)
Controls	398	103	13 (12.6%)	295	15 (5.08%)
<i>Nonwhite</i>					
Retarded	234	140	31 (22.1%)	94	12 (12.8%)
Controls	240	132	18 (13.6%)	108	10 (9.3%)

¹ World Almanac, 1990, p. 551.

INTERRACIAL DIFFERENCES IN REPRODUCTIVE CASUALTY

Pasamanick and Lilienfeld found from their Baltimore study, interestingly, nearly every nonwhite child with IQ <50 had been exposed to at least one maternal complication (Table 7-9) [415].

All four principal cells of Table 7-7 reflect higher cross affinity between maternal complications, low birth weight, and mental retardation but the relative ratios differ (Table 7-10).

Table 7-10
RATIO OF CROSS AFFINITY, MENTAL RETARDATION
TO CONTROLS, IN LOW BIRTH WEIGHT [415]

<i>Maternal complications</i>	
White	2.0397
Nonwhite	1.625
<i>No maternal complications</i>	
White	2.157
Nonwhite	1.384

These ratios extend and confirm what Table 7-8 points out, the effect of complications, including low birth weight *per se*, has less supplemental or additive effect in blacks or nonwhites than in whites. The interracial ratios for epilepsy (Table 7-8) exceed those for mental retardation (Table 7-10), as shown in Table 7-11.

Table 7-11
COMPARATIVE INTERRACIAL RELATIVE RISKS FOR EPILEPSY
AND MENTAL RETARDATION (WHITE:NONWHITE) [330]

	<i>Maternal complications</i>	<i>No maternal complications</i>
Epilepsy	3.442	1.887
Mental retardation	1.255	1.559

These second order ratios suggest the following as one interpretation. When there are no maternal complications, there is some higher risk for white infants for mental retardation and epilepsy, 55.9 per cent and 88.7 per cent respectively. By contrast, when maternal complications are present, the relative risk for whites against blacks is less when mental retardation is the outcome measure, 25.5 per cent. As with any ratio, the final figure may differ due to a change in either the numerator or the denominator. The largest disparity is for maternal complications and infantile epilepsy. Here white

children have a much higher risk: 244 per cent beyond that for nonwhites. Whatever factor(s) promote those injuries which eventuate in epileptic states for blacks, some or all are more aggressive, or more efficient, in whites. This difference begs for additional research, perhaps at a cellular level, since these kind of surveys give the appearance of having reached their limit for insight. As has been said, association is not causation.

From adequate neonatal records, children were rated as neonatally abnormal when convulsions, cyanosis, or asphyxia occurred. The data on neonatal abnormalities are probably not as meaningful as some other data, since fewer records were deemed complete (from 61 to 83 per cent). Nevertheless, among both white and nonwhite infants, the higher rates of neonatal complications among mentally deficient children are consistent with comparable findings on maternal complications and low birth weight. Among whites, neonatal abnormalities were more common in mentally deficient children ($p < 0.0005$) (Table 7-12), extending the general interracial principle noted above.

Table 7-12
CORRELATION OF ABNORMAL NEONATAL STATUS AND
SUBSEQUENT MENTAL RETARDATION, BY RACE [415]

	Total	Neonatal condition	
		Complications*	No complications
<i>White</i>			
Retarded	255	46 (18.04%)	209 (71.95%)
Controls	252	19 (7.54%)	233 (92.46%)
<i>Nonwhite</i>			
Retarded	195	15 (7.69%)	180 (92.31%)
Controls	196	12 (6.12%)	184 (93.88%)

*Convulsions, cyanosis, or asphyxia.

Once again, the ratios for nonwhites (blacks) are narrower than those for whites. Only the ratio for complications has any meaning here: for whites, 2.393, nonwhites, 1.257. The interracial ratio for controls is 1.232 and for mentally retarded infants, 2.346. It is remarkable that, despite fluctuations in the final ratio *per se*, the relational pattern persists: the greater difference from control values is for whites, and complications, whether maternal or neonatal, have a larger impact on whites as well.

Table 7-13 shows the frequency of neonatal abnormalities by race in the history of retarded infants for: (1) low birth weight, after excluding mothers with complications; and (2) excluding children underweight at birth and without maternal complications.

These are trends and not clear differences, an effect of the effort to parse out individual factors. When race is disregarded, the difference in frequency of neonatal abnormalities between the mentally retarded infants and their controls is $p = 0.05$.

Table 7-13
SUBSET FREQUENCIES OF NEONATAL ABNORMALITIES*
IN MENTALLY RETARDED CHILDREN [415]

Category	White		Nonwhite	
	Retarded (n = 404)	Controls (n = 416)	Retarded (n = 235)	Controls (n = 240)
Premature births without maternal complications	29 (7.18%)	15 (3.61%)	12 (5.11%)	9 (3.75%)
Neonatal abnormality without premature birth or maternal complications	19 (4.70%)	11 (2.64%)	3 (1.28%)	2 (0.83%)

*Convulsions, cyanosis, or asphyxia.

This low order of presumed statistical significance does not hide the matrix pattern of incidence and internal ratios (relative risk) seen in several other examples noted above. Table 7-14 gives the matrix ratios from Table 7-13.

Table 7-14
COMPARATIVE INTERRACIAL RELATIVE RISKS FOR MENTAL RETARDATION, LOW BIRTH WEIGHT, AND NEONATAL COMPLICATIONS (WHITE:NONWHITE) [415]

	Neonatal complications*	No neonatal complications
Low birth weight	1.405	0.963
Normal weight	3.672	3.181

* Convulsions, cyanosis, or asphyxia.

This particular data set suggests an important role for neonatal complications in white infants in the pathogenesis of mental retardation, in fact, more so than in the low birth weight infants. When the ratios are compared horizontally, however, the role of low birth weight, once again, must be taken into account as synergistic with neonatal complications. The relative risk ratio for low birth weight between complications and no complications is 1.459 and only 1.154 in term infants with normal birth weight.

Pasamanick, Knobloch, and Lilienfeld showed that pregnancy complications [410] and low birth weight [443] and the frequency of developmental

disabilities are associated with socioeconomic status. They showed the higher rates of reproductive casualty for persons of low income status, mostly nonwhites, can largely be attributed to more prevalent pregnancy complications and low birth weight [410] (Table 7-15). The major factor which predisposes low income populations to higher prevalence of developmental disabilities is malnutrition.

Table 7-15
PREVALENCE OF LOW BIRTH WEIGHT, MATERNAL
COMPLICATIONS, RACE, AND ECONOMIC RANK [410]

<i>Race</i>	<i>Economic rank*</i>	<i>Low birth weight (per cent)</i>	<i>Maternal complications (per cent)</i>
White	Top quintile	5.0	5.0
	Bottom quintile	7.6	14.6
Black	All mothers	11.4	50.6

*By standards of the mid-1950s.

Subsequent large scale studies have confirmed these findings: namely, the interracial differences in reproductive casualty are primarily due to the high rates of low birth weight and prematurity among nonwhites. Williams [564] identified 1,425,000 live births in California from 1966 through 1970 with data available on birth weight, gestation, race, and infant sex. Williams was able to demonstrate that the relatively high infant mortality rate in the United States was due to the high incidence of low birth weight [564]. The much higher infant mortality among nonwhites was attributed to the extremely high prevalence of nonwhite low birth weight. The author stated,

The position of the United States in international comparisons of infant mortality rates has deteriorated in recent years. It is suggested here that this result may in part be due to the relatively poorer levels of maternal nutrition and to less favorable socioeconomic environments. . . . Recent evidence indicates that the mother's nutritional status during the third trimester of pregnancy is far the most likely single cause for prenatal growth retardation. [564]

Williams would likely not express astonishment at the rise in the 1990s of relative low birth weight [609] or the continuing important differences in low birth weight and perinatal mortality between blacks and whites, which continues unabated today.

Much space in this book has been dedicated to the work over many years of this remarkable collaboration between Fischer, Harper, Kawi, Knoblock, Lilienfeld, Parkhurst, Pasamanick, and Rider, findings essentially forgotten. In summary, Pasamanick and his many associates identified a continuum of

reproductive casualty highly associated with low birth weight, a primary result of malnutrition and with complications of pregnancy, especially many which are etiologically related to malnutrition. In this way, two effects of poor malnutrition come back together synergistically to encumber and handicap the fetus, and when the newborn survives birth, interferes with growth, development, and maturation of the child.

In undertaking additional review in detail of this coordinated literature and viewing it both in retrospect and in the light of this author's personal experience in thousands of perinatal autopsies, the continuum is not only correct and relevant but the only means to understand the considerable difficulty we face in attempting classification of the anatomical findings into definable categories. The hierarchy of classification is another manifestation of hubris in seeking to force our human will on nature (several other terms, mostly stronger, also come to mind in this context).

Pasamanick and Knoblock concluded [414, p. 23],

It would seem apparent from examination of the data that a good deal of reproductive casualty is immediately preventible and that much of the remainder could in time be prevented if we begin to plan and institute our preventive measures as soon as possible.

This might be characterized as the *full optimism hypothesis* and approach to prenatal care. A decade later, a more cautionary note was being expressed [35].

Berger, in the 1970s [35], confirmed the insight of Pasamanick and Knoblock, who repeatedly advocated prevention of prenatal and paranatal complications which predispose to developmental disabilities. Ironically, since then, more attention has been put on the development of elaborate perinatal care centers than to primary prevention. Berger et al. studied nearly 300,000 births in North Carolina and powerfully concluded that perinatal death will not appreciably decrease, irrespective of the technological sophistication of intensive care centers, until the rates of low birth weight and prematurity decline [35]. What these centers have achieved, however, is to move the median birth weight for 50 per cent survival down to lower levels as well as the birth weight for effective viability. It is important to keep in mind that no human infant has ever survived *wholly on its own*. The construct of viability is a false measure. What we are discussing is the level at which trained assistance of attendants is to be applied and, perforce, the level of experience and training that is required. Such discussions quickly move to the cost of treatment contrasted to the dollars needed for prevention. Each generation of medical and pediatric leadership seems to require redefinition of this problem; the editorial remarks of Frank Boehm in 1983 [47] and the

cost summary report for 1992 from the Centers for Disease Control in 1995 [613] reasonably state the dilemma, as well as the frustration of many, including the present author, over our inability as a nation and a society to grasp the essentials of the problem. This is addressed in some further detail in the analysis of the Women-Infants-Childrens Supplemental Program (WIC) (Chapter 6, pp. 144-154).

Berger et al found 5.7 per cent of the white infants weighed $\leq 2,000$ g at <35 weeks of gestation or both [35]. For nonwhites, 14 per cent of births had the same attributes. It is noteworthy that neither the number of prenatal visits nor the level of competence of the obstetrical and neonatal care facilities at the hospital of delivery significantly affected the perinatal mortality rate. Berger et al. declared:

It appears that significant control of excess perinatal mortality among nonwhites will depend on prevention of prematurity. Since the prematurity rate for nonwhites has been increasing during the past two decades while that of whites has remained stable, the concept of preventing prematurity assumes even greater significance – There is little likelihood that regionalized perinatal care will have an impact on the race differential in perinatal mortality – It is apparent that at the time of delivery it is too late to change the degree of maturation of the infant.

Berger, in effect, concluded that other means must be found in order to improve pregnancy outcome; just having women come to a clinic for superficial assessment has little value, although it must be allowed the motivation expressed by doing so is a more positive force for gestational health than not doing so at all!

THE RELATION OF STANDARDIZED PRENATAL CARE WITHOUT PROACTIVE NUTRITIONAL ASPECTS

This fundamentally pessimistic view was echoed by Gortmaker in 1979 who found that the intensity of prenatal care had little to do with the outcome [207]. An earlier study, in 1974, by Terris and Glasser [523] came to a similar conclusion. More detailed analysis of their data identified differences in birth weight by the number of prenatal visits (Tables 7-16 & 7-17). This is an extremely interesting result. There is only one apparent positive finding: the proportion of low birth weight for *no prenatal care at all* (none) is 2.6 times greater than the proportion with >2501 grams at birth. This is treated in the table as the ratio mature:premature, 0.379, a stark contrast to all others which are in a narrow range, 1.140-1.255. The onset of prenatal care, at the level provided in 1974 and before, during the first to third months of pregnancy, had no effect on eliminating low birth weight *per se*. Birth weight distribution

Table 7-16
DISTRIBUTION OF BIRTH WEIGHT BY TIMING OF
FIRST PRENATAL VISITS (ADAPTED FROM [523])

<i>First visit month</i>	<i>Premature <2500 g</i>	<i>Mature ≥2501 g</i>	<i>Ratio of percentages (Mature:premature)</i>
None	996 (22.19%)	2378 (08.42%)	0.379
1-3	369 (08.22%)	2915 (10.32%)	1.255
4-6	1727 (38.47%)	12385 (43.86%)	1.140
7-9	1397 (31.12%)	10561 (37.40%)	1.202
Total	4489	28239	

remains closely similar thereafter. This tells us that a prenatal visit is better than none but also that it doesn't seem to make any difference when it happens! A more precise case comes from the details of Terris and Glasser's data [523] by birth weight for the infants ≤ 2500 grams (Table 7-17).

Table 7-17
RELATION OF FIRST MONTH OF PRENATAL CARE
TO LOW BIRTH WEIGHT (PERCENTAGES) [523]

<i>Month</i>	<i>Total</i>	<i>Birth weight</i>			
		≤ 1000 g	1001-1500 g	1501-2000 g	2001-2500 g
None	996	221 (22.19)	135 (13.55)	204 (20.48)	436 (43.78)
1-3	369	29 (7.86)	26 (7.05)	64 (17.34)	250 (67.75)
4-6	1727	114 (6.60)	152 (8.80)	303 (17.54)	1158 (67.05)
7-9	1397	11 (0.78)	73 (5.23)	241 (17.25)	1072 (76.74)

This breakdown indicates, seemingly and paradoxically, that the longer one waits to seek pregnancy care, the lower the risk of having an infant under 1000 grams birth weight. This ignores, as unascertainable by the study of surviving infants, those of very low birth weight who have died. The outcome for birth weights between 1001 and 1500 grams is less dramatic, with a confused result from 1 to 6 months, but a similar trend otherwise. The swing group is birth weights from 1501 to 2000 grams; it doesn't seem to matter at all, whereas late registration would seem to serve to bring the birth weight above 2000 grams, a trend confirmed in Table 7-16. The proportion of infants over 2500 grams achieved by registration in gestational months 7-9 is 88.27 per cent [523]. None of these studies considered nutrition as a factor in pathogenesis. This paradox is more likely to be explained once there is sufficient information on the biological basis for the most efficient maternofetal interaction leading to term infants of appropriate size and good health [5].

ASSOCIATION OF MENTAL DEFICIENCY WITH LOW BIRTH WEIGHT AND COMPLICATIONS OF PREGNANCY

Pasamanick and Lilienfeld examined the birth certificates and reviewed pertinent medical records of 639 singleton children born in Baltimore between 1935 and 1952 subsequently classified as mentally deficient, as measured by IQ <80 [415]. Birth weight, neonatal abnormalities, and complications of pregnancy were recorded. A control group was drawn by taking the birth which next followed according to hospital records which was consistent with sex, race, place of birth, and maternal age group. The personnel extracting the data did not know to which group any child belonged (study or control). The socioeconomic status of the study group was generally the same as the controls.

The frequency of multiple births in the study group was 3.2 per cent, about 2.5 times an unselected population prevalence of 1.25 per cent. The specific prevalence of multiple births in the accessioned control group was even lower, just 0.5 per cent. The authors tried to reduce inherent bias in the study on mental deficiency by excluding multiple births (see p. 160).

Several complications, especially toxemia, bleeding, and abruption of the placenta, were much more prevalent in the study group (Table 7-9). There were 91 cases of toxemia and eight of abruption of the placenta among mothers of the study group children versus 76 instances of toxemia and five of abruption among mothers of the controls. The higher rate of toxemia among study group children is significant at the 5 per cent level. There was no difference between the two groups regarding either duration of labor or delivery operative procedures (Table 7-9).

Low birth weights accounted for 17.1 per cent of mentally deficient children contrasted to 8.7 per cent for controls ($p<0.00005$). As is implied by the data in Table 7-9, the low birth weight incidence was significantly higher in the study group for mothers with complications ($p<0.005$) than among those who did not ($p<0.02$). Interestingly, almost identical rates turned up for maternal complications for epileptic children in nonwhite cases (Table 7-7).

Quite recently, Richmond et al. restudied obstetric management of fetal distress and its association with cerebral palsy [442]. Fetal distress was identified in 24 per cent of term infants born with cerebral palsy and in 11 per cent of "controls." The clinical response, on reconsideration, was inappropriate in 12 per cent of those with CP and only 3 per cent of the controls. Upon consideration, it was estimated that any link between "fetal distress" and cerebral palsy was a minor factor, if one at all, and that "optimum" management would reduce the risk by only 6 per cent overall.

RELATIONSHIP BETWEEN LOW BIRTH WEIGHT AND NEUROLOGICAL DAMAGE AND MENTAL DEFICIENCY

Knobloch, Rider, Harper, and Pasamanick conducted a well-controlled anteretrospective longitudinal study to determine the relationship between birth weight and neurological function and intellectual potential [288]. These were examined in 500 singleton, low birth weight children compared to a control group of 492 singleton term births but weighing $\geq 2,500$ g. All 992 children were born in Maryland in 1952 and lived in Baltimore at the time of the study. There were 57 surviving singleton infants born in 1952 at $\leq 1,501$ grams available for the study; a random sample of 443 infants weighing between 1,501 and 2,500 g at birth made up the remainder of the low birth weight group. The 492 normal weight controls were selected to match study infants for race, season of birth, hospital of birth, parity, and socioeconomic status. Knobloch et al. defined ten levels of socioeconomic status and all were represented in the study. There were 557 black and 435 white children, but results were merged because they could not distinguish test results by race after birth weight was adjusted for comparability. The results were stated under two headings, intellectual potential and neurological status. This summary will concern only the raw data for two reasons: (1) the adjusted figures hew closely to the values obtained for infants weighing 1501-2500 grams at birth, as expected since they make up 88.6 per cent of the whole, and (2) the adjusted group did not make use of the further stratification found in the raw data between subsets at 1501-2000, and 2001-2500 grams birth weight respectively.

Developmental, neurological, and physical examinations were performed on all 992 infants at postnatal ages ranging from 34 to 69 weeks. Seventy-five per cent of the examinations, including nearly all of the controls, were done within one week of age 40 weeks [288]. The exams of the low birth weight infants were age adjusted for degree of prematurity [288,290]. Almost all tests were performed by one pediatrician, who, along with all other examiners, was not aware of infant group assignments [288,290].

As evidenced by Tables 7-18 and 7-19, the prevalence of both neurological abnormalities and intellectual defects increased as birth weight decreased [288]. Knobloch et al. summarized the overall result in their Table 4 (p. 584). The total deviation from normal was 50.9 per cent for infants weighing ≤ 1500 grams, 24.5 per cent for infants weighing between 1501 and 2500 grams, and 12.8 per cent for infants weighing ≥ 2501 grams at birth. Moreover, the prevalence of both abnormal neurological status and impaired intellectual potential was progressively higher as birth weight fell.

Knobloch et al. identified the infants who were blind. They noted three

were blind from retrorenal fibroplasia with birth weights under 1501 grams; these three were amongst the 20 with the most severe brain injuries, cerebral palsy, other overt neurological abnormalities, or defined intellectual deficit, and combinations of the several categories. There were visually impaired infants from the larger group of lesser degree of brain injury: two blind and three with partial visual loss.

The neurological function of each infant was classified as one of the following: normal, indeterminate (probably normal), minimal damage (no overt abnormality), possible cerebral palsy, or overt neurological abnormality [288]. As Table 7-18 implies, infants with birth weight $\leq 1,500$ g had significantly more of all degrees of neurological abnormalities than either the 443 other low birth weight infants or the normal weight controls.

The tabular data from this paper [288], as contrasted with the follow-up report of Harper et al. [230], did not split out the intermediate groups 1501-2000 and 2001-2500 g birth weight.

Nevertheless, as is shown in the table, 26.3 per cent of the lowest birth weight infants had possible cerebral palsy or overt neurological abnormalities, whereas 7.2 per cent of the infants who weighed between 1,501 and 2,000 g at birth and only 1.6 per cent of the controls exhibited similar neurological impairment [288,290].

Table 7-18
STATUS OF NEUROLOGICAL DEVELOPMENT
AT POSTNATAL AGE, 39-64 WEEKS [288]

Birth weight	Number of infants	Neurological status		
		Normal or indeterminate function	Minimal brain damage	Possible cerebral palsy or overt defect
≤ 1500 g	57	29 (50.9%)	13 (22.8%)	15 (26.3%)
1501-2000 g	443	340 (76.7%)	71 (16.0%)	32 (7.2%)
> 2500 g	492	435 (88.4%)	49 (9.96%)	8 (1.6%)

Each infant's intellectual potential was designated by one of eight classifications: superior, high to average, average, low to average, dull to normal, borderline defective, defective, or overt defect (type unclassified) [288]. Similarly, Table 7-19 indicates gradations of intellectual potential, with more infants of higher potential as birth weight increased.

These are striking findings and intellectual potential perhaps more so. Not in Table 7-19 is the further datum that no infants with a birth weight ≤ 2000 g

was rated as superior; there were 31 in the 2500 g comparison controls (6.3 per cent). The data in Tables 7-18 and 7-19 demonstrate there is less than one chance in a billion that neurological function is not related to birth weight.

Table 7-19
INTELLECTUAL POTENTIAL ESTIMATED BY
EXAMINATION AT 39-64 WEEKS POSTNATAL AGE [288]

<i>Birth weight</i>	<i>Number of infants</i>	<i>Intellectual potential</i>		
		<i>Superior to high average</i>	<i>Average to dull</i>	<i>Borderline to defective</i>
≤1500 g	57	3 (5.3%)	44 (77.2%)	10 (17.5%)
1501-2000 g	443	72 (16.3%)	363 (81.9%)	8 (1.8%)
>2500 g	492	107 (21.7%)	377 (76.6%)	8 (1.6%)

Knobloch et al. observed the incidence of lesser degrees of neurological impairment was higher among the low birth weight infants and hypothesized that minor, often subclinical impairment frequently presaged significant abnormalities which might be diagnosed later in life [288]. As a result of further follow-up, they discovered those who had minimal brain damage as infants had such a tendency to develop behavioral and learning disorders later in life. Tests given at one year of age confirmed that minimal brain damage may be a precursor of overt neurological impairment [109]. These tests also revealed race, educational level of the parents, and socioeconomic status to be without any causal relationship to behavioral functioning.

Results of additional tests at age three years, similar to the ones given around age forty weeks, demonstrated the results of the initial exams were a reliable indication of later neurological function and cognitive potential [290]. The correlation between the results of the two tests was 0.5. Among children determined by the exams around age forty weeks to have neurological abnormalities or intellectual impairment, the correlation between results of initial exams and those from exams at three years of age was 0.75. In a subsequent study, Knobloch and Pasamanick showed these examinations of neurological function during infancy were and are highly predictive of central nervous system function in childhood [295], in contrast to testing later reported from the Collaborative Study [229].

Nine hundred out of the 992 infants in the longitudinal study just discussed were examined again at ages ranging from three to five years [230]. This indicated the relationship between low birth weight and mental deficiency to be more dramatic than was suggested by the initial exams around forty weeks of age [230]. Table 7-20 shows the degree low birth weight was associated with mental deficiency. The data in the total column

in parentheses is the original size of each group when tested around one year of age. There was little loss to follow up in any of the four groups.

Table 7-20
INCIDENCE OF MENTAL DEFICIENCY AT AGE 3 TO 5 YEARS [230]

<i>Birth weight</i>	<i>Total infants</i>	<i>Number with mental deficiency</i>	<i>Percentage</i>
≤1500 g	56 (57)	13	23.2
1501-2000 g	79 (84)	9	11.4
2001-2500 g	340 (359)	31	9.1
>2500 g	465 (492)	23	4.9

This illustrates rather clearly the inverse relationship between birth weight and the risk of mental deficiency.

Table 7-21 makes a similar, direct comparison for neurological status between 39-64 weeks and 3 to 5 years.

Table 7-21
COMPARISON OF NEUROLOGICAL STATUS*
DETERMINED AT DIFFERENT AGES [230]

<i>Birth weight</i>	<i>Ages 39-64 weeks</i>	<i>Ages 3-5 years</i>
≤1500 g	15/57 (26.4%)	13/54 (24.1%)
1501-2000 g	10/84 (11.9%)	7/76 (9.2%)
2001-2500 g	21/359 (5.8%)	22/330 (6.7%)
>2500 g	8/492 (1.6%)	23/444 (5.2%)

*Overt neurological deficiency and cerebral palsy.

There is little change in the frequency of neurological problems over the span of years for all births under 2500 grams, but there is a three-fold rise in the frequency for birth weight of mature infants. Indeed, this makes sense neurologically and biologically. The lower birth weight infants manifest their disturbed state early since they have less capacity for adaptation. Another factor of some importance is that possible lesser degrees of injury finally become manifest during the postnatal period of functional maturation, due to loss of collateral neural integration and feed back.

The Motherwell Protocol tracked children with severe mental handicap in concert with Health Board District records. The survey was through December 31, 1978, two years after the termination of detailed record keeping for the Protocol at Motherwell Maternity Hospital. The two tables which follow (Tables 7-22, 7-23) cover the overall area distribution of severe mental handicap and the frequency of Down syndrome in the region.

Table 7-22
PREVALENCE OF SEVERE MENTAL HANDICAP, CHILDREN
UNDER 16 YEARS, MOTHERWELL DISTRICT, WITH HEALTH
BOARD POPULATION ESTIMATES* OR CENSUS DATA.

<i>Locality/area</i>	<i>Age specific population</i>	<i>Severe mental handicap</i>	<i>Prevalence per 1000</i>
Motherwell District	41,583	97	2.33
Bellshill Subdistrict	21,583	62	2.87
Motherwell Burgh	20,000*	35	1.75
<i>Motherwell Burgh births</i>			
Delivery elsewhere	4,000*	13	3.25
Delivery, Motherwell			
Maternity Hospital	16,000*	22	1.375

The difference between Motherwell Protocol cases and delivery elsewhere in the Burgh, expressed as observed minus expected cases, is 6 in the Latin square table. This is a χ^2 of 6.4399, d.f. = 1, p = 0.0112. The difference between Motherwell Protocol cases and delivery at Bellshill Hospital, expressed as observed minus expected cases, is 12 cases, as above. This is a χ^2 of 8.5592, d.f. = 1, p = 0.0034. The success of the Motherwell dietary protocol, graded as it was, nevertheless was the principal difference in the pregnancies of this part of Scotland, and involved a substantial share of the births between 1960 and 1976. One result was a statistically significant decrease in severe mental handicap for children under the age of 16 years, the duration of the active dietary protocol.

Interestingly, figures from the Lanarkshire Local Authority Areas on Down syndrome reveal a similar generally favorable result for the offspring of mothers in the Protocol (Table 7-23).

These results deserve comparison to the prevalence of Down syndrome in

Table 7-23
DOWN SYNDROME IN LANARKSHIRE LOCAL
AUTHORITY AREAS AS OF DECEMBER 31, 1978

<i>Local Authority</i>	<i>Number of cases Down syndrome</i>	<i>Rate per 1000 population</i>
Cumbernauld	17	0.93
East Kilbride	26	1.08
Hamilton	36	1.20
Lanark	15	1.07
Monklands	23	0.71
Motherwell	24	0.55

the United States [611]. This recent review from the Centers for Disease Control identified considerable variation in the frequency of Down syndrome in various parts of the country and for different demographic groups (Table 7-24).

Table 7-24
PREVALENCE OF DOWN SYNDROME, UNITED STATES, 1983-1990 [611]

Number of births in survey (circa 25 % of national total)	7.8 million
Rate	1:1087 births
Lowest area (Kansas)	5.9/10,000
Highest area (Colorado)	12.3/10,000
Hispanic	11.8/10,000
White	9.2/10,000
Black	7.3/10,000

Since Down syndrome is determined by a genetic process during meiosis, late pregnancy nutritional programs would have no effect, but one is reminded of the report of Dieckmann [135] in which high protein intake gave the appearance of eliminating spontaneous miscarriages. The only way these situations could be related is from a carry forward effect on general health from previous dietary improvement and enhancement of the ovarian environment. The rate of Down syndrome in children of mothers in the Motherwell Protocol was the lowest in the region, about half of the composite rate for the other local authority areas.

COMPLICATIONS AND LOW BIRTH WEIGHT ASSOCIATED WITH READING DISORDERS

Kawi and Pasamanick, in a study of 205 white males aged 10 to 14 years with reading disorders but no intellectual impairment (each had an IQ ≥ 85), showed that complications of pregnancy, low birth weight, and neonatal abnormalities were highly associated with the development of reading disorders [277]. The authors formed a control group of 205 children by selecting the birth following that of each respective study group child, after controlling for place of birth, sex, race, and maternal age group. As might be expected from this approach, there was virtually no difference in socio-economic status between study and control groups. Staff extracting the data from the prenatal and hospital records were not aware of which group the children represented.

Hypertension, bleeding, and toxemia were the complications most frequently found among mothers of children with reading disorders. Bleeding and toxemia [106], in addition to abruption of the placenta, can result in neurological sequelae. It is noteworthy that 16.6 per cent of mothers of study group children had at least two complications and 6.3 percent had three or more complications during the index pregnancy (Table 7-25). In comparison, only 1.46 per cent of control children were exposed to two maternal complications; none of their mothers had more than two complications.

Table 7-25
ASSOCIATION OF PREGNANCY COMPLICATIONS, INDEPENDENTLY AND CUMULATIVELY, AND DELIVERY, WITH READING DISORDERS [277]

<i>Complication</i>	<i>Study group</i>	<i>Control group</i>	<i>Value of p</i>
None	128 (62.44%)	161 (78.54%)	0.001
One or more	77 (37.56%)	44 (21.46%)	0.0001
Two or more	34 (16.58%)	3 (01.46%)	0.0001
Three	13 (06.34%)	0 (00.00%)	0.001
Total cases with complications	124	47	
Placental abruption	2 (00.98%)	0 (00.00%)	NS
Bleeding	21 (10.24%)	7 (03.41%)	0.01
"Toxemia"	20 (09.76%)	8 (03.90%)	0.02

NS = Not significant statistically.

Dividing the study group into the 103 best readers and the 99 worst readers (three unclassified), the frequency of complications was found to be much higher among the mothers of the worst readers [277]. They noted that the greater the reading disability, the more frequent were complications [414].

The incidence of low birth weight was 11.7 per cent among children with reading disorders in contrast to 4.4 per cent among controls ($p < 0.02$) [277]. As shown in Table 7-26, the differences between study and control groups for low birth weight when related to obstetric complications are especially noteworthy.

The incidence of low birth weight, whether complications were present or absent, was significantly higher among the children with reading disorders. Note that in the study group the incidence of low birth weight among mothers who had complications (17.7%) was 139 per cent higher than for mothers with no complications (7.4%). In contrast, for controls, the low birth weight from mothers with complications (3.2%) was 37 percent lower than for cases with no maternal complications (5.06%).

Table 7-26
RELATION OF LOW BIRTH WEIGHT, SINGLY AND IN COMBINATION
WITH OBSTETRIC COMPLICATIONS, WITH READING DISORDERS [277]

Category	Reading disorders		<i>p</i>	Excess of finding in study group
	Study group (N = 205)	Controls (N = 205)		
Low birth weight	24 (11.7%)	9 (04.4%)	0.02	150%
Complications	124 (60.5%)	47 (22.9%)	0.00001	164%
No complications	81 (39.5%)	158 (77.1%)	0.00001	n.a.
<i>Subcategories from either of the above:</i>				
Low birth weight				
from mothers with complications	22 (17.7%)	4 (03.2%)	0.0001	450%
Low birth weight from mothers without complications	6 (7.4%)	8 (5.06%)	NS	46%
Low birth weight and complications	14/205 (6.8%)	1/205 (0.5%)	0.005	1300%
Low birth weight, no complications	10/205 (4.9%)	8 (3.9%)	NS	26%

More striking differences between the study and control groups can be found by comparing the cases in which the mothers had at least one complication and delivered a low birth weight baby with those in which a low birth weight child was born to a mother who did not have complications (Table 7-26). As expected, the low birth weight incidence was higher among the study group children whether complications were present or absent. In the study group, the incidence of cases in which a mother had complications and gave birth to an underweight baby (6.6%) was 35 per cent higher than that of cases in which the mother had no complications but delivered a low birth weight child (4.9%). Significantly, among the controls the incidence of the former cases (0.7%) was 82 per cent *lower* than that of the latter (3.9%). Whereas the frequency of births of underweight children who were not exposed to maternal complications was only slightly higher (26%) in the study group than in the control group, the frequency of low birth weight children who had been exposed to at least one complication of pregnancy was more than nine times higher among the children who had reading disorders. Thus, there is a synergistic effect between low birth weight and maternal complications which predisposes to reading disorders, even for children of normal intelligence. As can be extrapolated from the results of

several of the studies reviewed in this chapter, comparable thorough analysis of children with neurological impairment would probably yield results in accord with these.

Twice as many children in the study group experienced neonatal convulsions, cyanosis, or asphyxia ($p < 0.05$). It is significant that normal birth weight children not exposed to maternal complications did not develop reading disorders, despite neonatal complications (Table 7-27), specifically convulsions, cyanosis, or asphyxia.

Table 7-27

RELATION OF NEONATAL COMPLICATIONS AND READING DISORDERS ASCERTAINED LATER BY TESTING [277]

	<i>Study group</i>	<i>Controls</i>
Number of children	205	205
Children with neonatal complications	16 (7.8%)	8 (3.9%)
Birth weight > 2500 g with neonatal but no maternal complications	6 (2.9%)	6 (2.9%)

The overall frequency of children exposed to complications during either prenatal or paranatal periods (viz, maternal and neonatal complications) was 45.4 per cent in the study group and 28.2 per cent in the control group ($p < 0.0001$). Significantly, Kawi and Pasamanick discovered that neither maternal age nor parity accounted for the differences in birth weight, neonatal abnormalities, or maternal complications either in or between the study and control groups as factors in reading disability [277].

Chapter 8

THE RELATION OF MATERNAL HEALTH TO INFANT HEALTH AND DEVELOPMENT

COMPLICATIONS OF PREGNANCY, like low birth weight, have been associated with malnutrition. Reducing the effect of serious pregnancy-related complications, such as gestosis, placental abruption, placenta previa, and dystocia, would reduce risks of developmental disabilities. The Collaborative Study was designed to "prevent mental retardation, congenital malformations, cerebral palsy, and handicapping neurosensory defects . . . [and to] . . . provide knowledge on the relationship between perinatal factors and the subsequent development and cause of abnormalities in the offspring." Data from prenatal records of 39,215 pregnant women in the program revealed high correlations between nutrition-related complications of pregnancy, birth weight, and neurological damage in infancy [402].

Unfortunately, data from the mammoth study must be interpreted with decided reservation. Although many of the 16,693 exclusions (29.9% of the 55,908 cases initially registered) were justified and actually necessary for an accurate analysis of effects of various maternal characteristics and factors associated with childbirth on the outcome of pregnancy, numerous defects in the design and especially the operation of the study, limit its usefulness. A serious omission, effectively disqualifying, is the lack of any information on maternal nutrition despite reams of numbers on minor points, such as hypothyroidism, glomerulonephritis, other rare diseases, the third stage of labor, and so forth. This was discussed in a preliminary way in the introduction to this book. The period of data collection (January 2, 1959, through December 31, 1965) was marked by redefinition of methodology, sampling ratios, and other characteristics which should have been precisely specified and maintained throughout, for consistency [402]. It would have been better

to develop a database which held coherence despite some degrees of incompleteness. In addition, much data was deleted because of improper reporting. There was such a lack of conformity in the data collected by the 14 participating hospitals (affiliated with 12 universities) a great deal of it was incongruous relative to the institutions, and it was discarded. One center experienced a 16.4 per cent loss of cases due to no follow-up. Furthermore, numerous cases were excluded from analyses without explanation.

It is of special interest that the most important test used, the neurological examination given at age one, has been shown to lack reliability, when compared with more comprehensive methods [295]. The authors of the second book, *The First Year of Life*, [229] asserted the achievement of ". . . high success in follow-up with carefully conducted developmental assessments in later childhood (p. xvii)," but in actual fact, for example, the modified Bayley Scales of Infant Mental and Motor Development, applied as close as practicable to the eighth month "birthday," were applied to 11,534 white and 13,516 black infants. There were 55,908 women initially registered in the study. This is a case loss ratio of 0.552, surely not high success. Similarly, the one-year exams were administered, for neurological status, to 12,703 white and 15,142 black infants, a case loss ratio of 0.502, not much better.

A premise of this book is data with some coherence, and biological meaning beyond first order plausibility, should be accorded weight despite some faults of given studies or protocols. This principle can be applied here and some results are of interest to reproductive casualty and are important as well. Whether the \$100 million was entirely well spent will be left to the minions of the General Accounting Office, no friend of government waste.

The Collaborative Study identified placenta previa in 0.75 per cent of pregnancies. There were 142 examples in 18,446 white and 110 examples in 19,689 black placentas. Another instance of lost data appears in the data tables for placenta previa [402, p. 407]; there were 1,080 placentas for which the status of previa or not was unknown, a 2.6 per cent data loss.

This complication was highly associated with low birth weight (presumed prematurity, in part) despite the observation by Rizos et al. [445] on progressive reduction in the frequency of previa as gestation advances, through placental migration. The frequency of low birth weight in previa was 32.8 per cent for whites and 52.9 per cent for nonwhites.

Abruptio of the placenta complicated 2.1 per cent of the 38,453 specimens. The frequency of low birth weight in abruptio was 26.3 per cent for whites and 47.7 per cent for blacks. The incidence of definite neurological damage, determined at one year of age, was twice as high for infants born from a pregnancy with abruptio of the placenta.

The incidence of neurological damage was three times higher among low

birth weight infants. The greater prevalence of neurological damage among nonwhite infants was accounted for by more nutritionally related complications and low birth weight, a finding concordant with previously mentioned studies.

The prevalence of cerebral palsy among classifiable disabilities is low. Alberman, following the scheme of Drillien [151], reported on the proportion of disabilities and prevalence of cerebral palsy (Table 8-1) [9].

Table 8-1
CEREBRAL PALSY WITHIN CLASSIFIABLE DISABILITIES OF LOW BIRTH WEIGHT INFANTS, ACCORDING TO THE CRITERIA OF DRILLIEN [9,151]

<i>Birth weight class</i>	<i>Classifiable disabilities</i>	
	<i>Proportion of cases</i>	<i>Prevalence in population</i>
≤1500 g	0.326	0.052
1501-1750 g	0.278	0.029
1751-2000 g	0.184	0.013

Puerperal infection was associated with a greater than 50 per cent increase in neurological abnormalities. Goodlin recently called for a thorough review of the criteria for the definition of cerebral palsy, in part to distinguish varied pathogenesis [205].

Langlois studied the mass of the human uterus and pointed out that standard references prior to 1970 used autopsy data only with few women before menopause [307]. He took cases from a large surgical pathology service and sought to correlate age, gravidity, parity, and race to uterine weight. He found, perhaps not surprisingly, the weight of the uterus rose with increased gravidity and parity, and, in somewhat colinear fashion, with age up to 50 years. The part of the study which deserves further examination is the data on the prepregnancy uterine base weight and the effect of gestation continuing to the threshold of fetal *viability* (defined as >20 weeks).

The nulliparous gravidas (one pregnancy only, not to second half of pregnancy or to term) were the key to showing a potentially important difference between white and black women (Table 8-2). In other words, the never pregnant black uterus is almost half again as heavy (1.496 times) as the white uterus. The mass and the relative ratio between whites and blacks do not change if the first pregnancy fails to exceed 20 weeks of gestation. The critical key is the third point in the data: a first pregnancy to viability/term changes the future nonpregnant mass of the uterus; the white uterus increases to residual mass equal to 1.84 times the *baseline*, but the black uterus increases only 1.23 times. The implied question is, does this mean gestational adaptation of the uterine vasculature is limited to the same degree? Is this a

Table 8-2
UTERINE WEIGHT DIFFERENCES BETWEEN WHITES AND BLACKS [307]

<i>Gravity</i>	<i>Parity</i>	<i>White</i>	<i>Black</i>
0	0	49.0 ± 5.1	73.3 ± 5.8
1	0	49.9 ± 4.7	73.3 ± 4.7
1	1	90.4 ± 8.7	90.5 ± 13.2
Racial differences:			
Nulligravidas:		0.01 > p > 0.001	
Nulliparous primigravidas:		p = 0.002	
Primiparous primigravidas:		p > 0.5	

factor in the greater risk for gestosis, preterm labor, and low birth weight for pregnant black Americans? Langlois did not reach for answers to these or related questions; he was seeking to provide an improved, more realistic database for uterine size and weight. His paper succeeds in that objective [307]. In addition, it offers insight into some engaging possibilities for future research and consideration.

These patterns of uterine growth in pregnancy may influence vascular connections in early placentation [80,491].

MATERNAL COMPLICATIONS

Numerous studies, some reviewed here, show that sound maternal nutrition provides the best assurance for uncomplicated deliveries of healthy children. Contrary to some beliefs, the births of high birth weight children born to well-nourished mothers do not present obstetrical difficulties. For example, in one prospective study in which supplements significantly increased birth weight, there was no increase in the rate of dystocia [219]. There are always limits, of course. The Collaborative Study offered no subset risk figures when birth weight exceeded 2501 grams [402]. Lubchenco et al. with a database comparable to the Collaborative Study, did show a small rise in neonatal mortality when birth weight exceeded 4,000 g [343]. We need to distinguish here infants of diabetic mothers who have the burden of metabolic dysfunction added to their size [416]. Other studies indicate macrosomic infants do have increased birth complications at all gestational ages, including birth trauma and shoulder dystocia [6], situations which have been used to justify increased use of abdominal section [308]. The fetal weight threshold for the diagnosis of macrosomia has been variously stated as >4,000 or >4,500 g [308,319].

Complications of labor and delivery occur with underweight fetuses,

principally due to ineffectual dilation of the cervix and poor preparation of the vagina. The head of premature infants is more susceptible to trauma in *otherwise normal* labor and delivery, which lesions have been attributed often principally to "anoxia [64,350,479]." These aspects may be intensified when labor is precipitate.

The relationship between complications of labor and delivery, birth weight, and subsequent neurological development was documented in the Collaborative Study [229,402] and several other studies. Low birth weight occurred three times more often among women with a prolonged latent phase of the first stage of labor, i.e., more than 48 hours elapsed from rupture of membranes to the onset of active labor. This was in contrast to relatively spontaneous deliveries, when labor began less than 24 hours after membrane rupture [402]. The prevalence of neurological abnormalities was twice as common in infants from women in the former group.

Burke, analyzing the effects of prenatal diet in the second and third trimesters of pregnancy, showed that sound nutrition prevented many complications of pregnancy and labor [78]. As emphasized previously, all professional examinations were fully independent of one another [76-78]. As Table 8-3 shows, women on a good or excellent prenatal diet did not have toxemia. Statistically, the differences are highly significant ($p < < 0.0001$). Burke observed that toxemia did not occur when daily protein intake was at least 68 g.

Table 8-3
INFLUENCE OF PRENATAL DIET ON PREVALENCE OF TOXEMIA [76,78]

<i>Quality of diet</i>	<i>Women</i>	<i>Toxemia</i>
Excellent or good	31	0 (0.0%)
Fair	149	12 (8.1%)
Poor	36	16 (44.4%)

Additionally, no woman on a good or excellent diet had section delivery, whereas four (11.1%) of poorly nourished women required section for delivery. This might seem like a low percentage in 1999; Burke's papers are from 1943 and 11.1 per cent was definitely a high frequency. Comparable rates at some major hospitals, such as Duke Hospital in Durham, North Carolina, in 1943, would have been around 1.0 per cent. Major complications of labor and delivery were 50 per cent more frequent among mothers on poor to very poor diets. This was so despite an average *greater* infant weight of 1,219 g in the latter. Such data cannot be construed to support the proposition that more complications occur because the infant is small but they do support the interpretation that poor nutrition *in concert* with low birth

weight contributes to obstetric difficulty as well as to neonatal injury.

The relation of prenatal maternal nutrition and complications of pregnancy and delivery were shown by Ebbs' prospective study of 380 pregnancies [155,156]. The study was carried out under conditions of professional independence comparable to those of Burke. One hundred twenty women on poor diets had many more complications during pregnancy, labor, and delivery. One control group of 90 received food supplements. One hundred seventy well nourished women given nutritional education made up a second control group. The prevalence of complications was slightly lower in the fully supplemented (and educated) group than in the good diet group, but this was not significant. Ebbs' data show unequivocal benefit from prenatal nutrition for the outcome of pregnancy. The major complications in Table 8-4 are mostly anemia and toxemia [156]. The frequency of toxemia was over twice as high among 120 poorly nourished women than in either control diet group [155].

Table 8-4
INFLUENCE OF DIET ON COMPLICATIONS OF PREGNANCY [155,156]

<i>Quality of diet</i>	<i>Women</i>	<i>Without complications</i>	<i>Major complications</i>	<i>p*</i>
Good	170	82 (48.2%)	21 (12.4%)	10^{-6}
Supplement	90	41 (45.5%)	8 (8.9%)	10^{-5}
Poor	120	36 (30.0%)	43 (35.8%)	--

*Against poor diet consequences.

The duration of labor and postpartum recovery were greatest in the women in the poor diet group [156]. Marked dystocia was observed in 24.2 per cent of women on poor diets. In contrast, only 2.3 per cent of women on supplemented diets and 5.9 per cent on good diets had difficult labor [156]. In addition, the average duration of labor was five hours shorter in the good diet group than in the poor diet group [155].

Women with poor diets had many more (11.3% versus 2.4%) puerperal complications, such as heavy lochia, anemia, and other minor problems [64]. These complications, like the prenatal ones, were noted by an obstetrician unaware of diets of the 380 women.

Ebbs et al. concluded:

During the whole course of pregnancy the mothers on a good or supplemented diet enjoyed better health, had fewer complications and proved to be better obstetrical risks than those left on poor prenatal diets. [155]

In a prospective study of 750 pregnant women given nutritional education and vitamin supplements, Tompkins showed toxemia is due to malnutrition

[533]. As shown in Table 8-5, there were no cases of preeclampsia or eclampsia among the well-nourished women. In contrast, 750 controls (women at the same clinic but receiving neither dietary counseling nor supplementation), included five eclamptics and 59 women with gestosis; the difference is highly significant ($p < 0.00001$). All of the study group women with mild toxemia (4.0%) had only hypertension, not true toxemia.

Table 8-5
INFLUENCE OF PRENATAL DIET ON PREVALENCE OF TOXEMIA [533]

	<i>Study group (supplements and education)</i>	<i>Control group (Neither)</i>
Number	750	750
Eclampsia	0	5 (0.67%)
Preeclampsia	0	59 (7.87%)
Mild toxemia	30 (4.0%)	120 (16.0%)

Eradicating toxemia using principles of scientific nutrition, Tompkins declared:

All toxemias are the result of an underlying nutritional inadequacy which has not been recognized or controlled . . . The so-called toxemia of late pregnancy is in reality a nutritional deficiency state. [533]

Comparable results were obtained by Higgins of the Montreal Diet Dispensary in her analysis of 1,736 births which benefited from maternal nutritional education and, in 1,250 of the cases, nutrition supplements. For the 1,736 mothers, the rate of toxemia was 69 per cent lower than in other public patients and 39 per cent lower than in private patients receiving prenatal care at the same hospital [431]. In addition, for diet dispensary women, who generally delivered larger infants, there were more spontaneous deliveries and fewer sections than for either the other public or the private patients [431].

A deficiency of even one essential nutrient, besides possibly causing permanent neurological impairment in the newborn, can lead to complications during labor and/or delivery. In Robinson's study of 1,019 pregnant women, such complications was much higher among women restricted in their sodium intake [448].

Other studies have confirmed the relationship between salt intake and ease of delivery [51].

Bacola et al. documented the association between toxemia and prematurity and mental retardation [16]. In each of nine cases of mental

retardation in children with birth weight $\leq 1,500$ g, the child had severe RDS or late apnea, or the mother was toxemic. Of six infants born to five toxemic women, four (67%) were mentally retarded, and only one had normal intelligence. In contrast, among 34 low birth weight children with non-toxemic mothers, five (15%) were mentally retarded, and 19 (56%) had normal intelligence. The authors observed that mentally retarded children were associated with either pregnancies of very short gestation in which the mother did not develop toxemia or a longer, but usually less than the normal, period of gestation which became toxemic. The data in Table 8-6 reflect the virulence of toxemia (in one pregnancy the duration of gestation was unknown).

Table 8-6
RELATION BETWEEN LENGTH OF GESTATION,
TOXEMIA, AND MENTAL RETARDATION [16]

Length of gestation	Number of children	Number retarded children	Toxemic mothers with retarded children
<211 days	17	5 (29.4%)	0 (0.0%)
211-238 days	15	1 (6.67%)	1 (100.0%)
239-257 days	7	3 (42.9%)	3 (100.0%)
Total	39	9 (23.1%)	4 (44.4%)

In addition, in their study of 48 low birth weight infants who weighed at least 1,501 g at birth, Bacola et al. noted toxemic women often give birth to underweight term babies [17].

Drillien also observed that low birth weight was significantly associated with complications of pregnancy [150]. Among 400 low birth weight infants, maternal complications involved 52 per cent. In contrast, only 10 percent of well matched controls, mothers of normal weight infants, had complications.

Lubchenco studied 63 infants, none weighing $> 1,500$ g at birth. There were three instances of abruptio placentae [342]. Complications occurred during delivery in 62 per cent of the births.

Proteinuria during pregnancy, often seen in toxemic women in the last trimester, is commonly associated with the birth of developmentally disabled children. Proteinuria may antedate preventable neurological dysfunction. A 1969 National Institutes of Health retrospective study found proportionately more mentally retarded children among proteinuric pregnant women [452].

Rosenbaum et al., in a retrospective study, sought to determine whether proteinuria in the second half of pregnancy is associated with the birth of neurologically abnormal infants, even in the absence of other complications

[452]. Women were selected with (1) moderate or severe proteinuria (at least 3+) during or after the 24th week of gestation, (2) no hospitalizations before delivery, and (3) did not have hypertension (defined as diastolic blood pressure ≥ 90 Torr at one or more prenatal visits) or overt toxemia. Fifty-one women had given birth to 53 children. The children were examined by motor and mental tests, administered by a psychologist, at the age of eight months or an IQ exam at four years, or both. Some examples of maternal proteinuria were not classified as to basis, but six were associated with late pregnancy edema, possibly joint signs of preeclampsia. Sixteen women had definite and seven questionable urinary tract infections: few of these would likely have toxemia, but the conditions can coexist.

All 53 infants were matched with a control on the basis of sex, race, hospital of birth, birth order, maternal age, and a ranking of socioeconomic status. Each control infant was born to a mother of no higher socioeconomic status than his counterpart.

Five of the 53 study infants (9.43%) had definite neurological impairment and only one (1.9%) of the controls showed similar abnormalities. As expected, average birth weight and period of gestation were both higher in the control group.

The study infants scored significantly lower on the eighth month mental and motor exams. The average IQ for the 53 infants of the proteinuric mothers was 84.3 against 100.6 for the controls. For both the mental and IQ tests, the difference in scores between the two groups was significant at the 0.1 per cent level. Furthermore, infants in the study group scored lower on a neurological posturing factors examination which was given at age one year ($p < 0.05$).

The more severe the proteinuria, the greater the impairment in both mental and motor impairment. Eleven of 51 mothers had 3+ proteinuria on at least two occasions. Their infants scored much lower than the other 42 infants on the mental, motor, and IQ exams.

DEPENDENT AND INDEPENDENT ASSOCIATIONS OF BIRTH WEIGHT WITH DEMOGRAPHIC FACTORS

Wiener and Milton studied demographic correlates of low birth weight in approximately 108,000 live births in Baltimore from 1961 to 1965 [560]. Multiple births and births of less than 21 and over 48 weeks gestation were excluded. Approximately 9,100 births were excluded; 26.8 per cent were underweight, confirming the common experience that many twins or triplets have low birth weight. The distribution, undoubtedly, would have been higher, if births of abnormally long gestation had been considered

separately. The low birth weight incidence among whites was 7.7 per cent (8.5% if the excluded births were included); low birth weight among non-whites accounted for 14.6 per cent of births (16.7% including previously excluded births).

In order of descending degree of correlation, the independent demographic correlates of low birth weight were (1) length of gestation, (2) race, (3) trimester of first prenatal visit, (4) status of legitimacy, (5) socio-economic status, (6) maternal age, and (7) parity. All of these variables, many directly or indirectly associated with nutritional status, were associated with low birth weight at $p = 0.0001$. Multiple regression analysis indicated parity and legitimacy were the least related to low birth weight rate. Age, except for women under age 15, was also not related to low birth weight. The low birth weight prevalence for the highest risk population, as defined by these other factors, was 31.5 per cent.

SIGNIFICANCE OF PRE-PREGNANCY WEIGHT AND WEIGHT GAIN DURING PREGNANCY

An analysis of birth weight data from major studies in which nutrition-related variables are included demonstrates such factors as race, trimester of first prenatal visit, legitimacy, socioeconomic status, and parity show little or no independent association with birth weight. A multivariate analysis of data from the Collaborative Study indicated prepregnancy weight and weight gain during pregnancy were the two maternal factors most highly correlated with birth weight [402]. Of these, pregnancy weight gain had the larger influence, a point later confirmed by Rosso [460].

Prepregnancy weight is at best a crude indication of nutritional status. A woman who is not underweight (for body size) at conception has caloric reserves which protect her somewhat and her fetus from mild caloric deficiency. Consequently, birth weight is correlated with maternal prepregnancy weight. However, prepregnancy weight is not a good indicator of maternal health and intake of essential nutrients. It is not significantly associated with the continuum of reproductive casualty. Birth weight is a more reliable indicator of the outcome, but these points by themselves leave out the necessary and critical middle parts of the equation. Tompkins and Wiehl, in a retrospective study, found a significant relationship between substandard weight at conception and both the development of toxemia and the occurrence of low birth weight [533,534]. Prepregnancy weight and the proportion of normal birth weight ($>2,500$ g) were highly correlated ($p<0.005$) [533]. The same significance was found for differences in birth weight and birth length

between infants delivered by women at least 20 per cent underweight at their first prenatal visit and those born to mothers of normal weight. The essence and unidirectional nature of this relationship were later confirmed by Rosso [460,462]. As Table 8-7 reveals, the most underweight women had low birth weight infants four times more often than mothers at least 20 per cent overweight ($p<0.001$). Tompkins and Wiehl found pregravid weight more related to birth weight than gestational duration.

Table 8-7
PRE-PREGNANCY MATERNAL WEIGHT AND
FREQUENCY OF UNDERWEIGHT INFANTS [535]

<i>Weight status at first prenatal visit</i>	<i>Number of women</i>	<i>Low birth weight (percentage)</i>
≥20% underweight	65	10 (15.38)
5-19% underweight	444	37 (8.33)
Normal weight ± 5%	455	26 (5.71)
>5 to 19% overweight	364	16 (4.4)
≥20% overweight	237	9 (3.8)

In a prospective study of 839 pregnancies, Tompkins and Wiehl confirmed the relationship between prepregnancy weight and birth weight [535]. The difference in low birth weight between women at least 15 per cent underweight at their first prenatal visit and those within 5 per cent of standard weight is significant at the 1 per cent level (Table 8-8). Both the retrospective and the prospective studies suggest the underweight women were poorly nourished and registered for prenatal care later in pregnancy. These and other factors can appreciably increase the risk of having low birth weight children.

Table 8-8
PREGRAVID MATERNAL WEIGHT AND RISK OF LOW BIRTH WEIGHT [535]

<i>Prepregnancy maternal weight</i>	<i>Number of women</i>	<i>Low birth weight (percentage)</i>
≥15% underweight	157	21 (13.38)
±5% of standard weight	455	26 (5.71)

As stated previously, gestational weight gain is a proxy for nutritional status. However, two exceptions preclude gestational weight gain as a reliable proxy for nutritional intake. Undernourished, especially protein deficient, pregnant women can gain a lot of weight rapidly, in a relatively short time, as a result of fluid accumulation, often manifest as clinical edema.

The edema in such women, at risk of developing toxemia in late pregnancy, is a direct consequence of lower colloid osmotic pressure in plasma caused by hypoalbuminemia [56,515]. Also, as without pregnancy, a high weight gain may result simply from high caloric intake, which may lack essential nutrients. Assessment of nutritional status is best accomplished by analysis of blood constituents, which is not practicable in regular prenatal care. The alternative, taking a detailed dietary history, is a superior method of evaluating nutritional status. Actually, nutritional status might best refer to individual nutritional requirements more than to total dietary intake [534,561]. Although true in every sense, it is a complex problem. Perhaps future prenatal care will regularly have computer-based dietary analysis, activated by the mothers from a detailed check list at appropriate intervals. This would not be beyond currently available computer capacity.

Nutritional mismanagement is most frequent in obese patients [286]. The insistence that women lose weight or gain a minimal amount, when obese, is a major cause of iatrogenic reproductive casualty [424]. Kitay, in discussing the responsibility of the physician in ensuring proper nutritional intake by obese patients, declared:

Perhaps the most notorious problem in dysfunctional nutrition prevalent in modern obstetrics lies in the area of obesity . . . The obese pregnant patient should not be managed any differently, with respect to good nutrition, than her nonpregnant sister. **Education in the proper foods to eat**, rather than weight reduction, should be paramount during pregnancy. [286]

Tompkins and Wiehl demonstrated that weight restriction during any trimester of pregnancy can lead to toxemia or low birth weight or both [534]. They theorized that indiscriminate weight control led to nutritional deficiencies with concomitant catabolism:

In order to accomplish such a drastic restriction (12 to 15 pound weight gain) in a normal weight patient's gain in weight, there would have to be dangerous limitations established in regard to essential nutrients as well as actual caloric intake. These caloric restrictions would obviously have to be well below basal requirements, let alone those needed for the maintenance of energy requirements during pregnancy, and for fetal growth. There can be no rationale in any procedure which is predicated on such a process. [534]

In a subsequent study, they documented the significance of weight gain during pregnancy in preventing low birth weight [535]. Since they did not control for other factors which also influence birth weight, it is possible that weight gain might reflect other factors rather than be a primary force in preventing underweight births. Consequently, neither prepregnancy weight nor weight gain should be construed as primary factors in reducing reproductive casualty. Emphasis should be on prenatal maternal nutrition, as

the biologic basis for substantial fetal weight gain.

Low birth weight among women, those with prepregnancy weight more than 5 per cent below standard weight and gaining less than average weight by 24 to 26 weeks of gestation, was 20.0 per cent, a very high frequency (Tables 8-9 and 8-10) [535]. In contrast, women within 5 per cent of standard weight at the first prenatal visit, receiving 50 g protein plus vitamin supplements, and gaining substantial weight during pregnancy (the best nourished), delivered less than 2 per cent infants with low birth weight.

Since full-term, healthy children are born to women who have a normal pregnancy irrespective of weight gain, subjecting a group of women to any particular weight control regimen is unscientific and potentially hazardous [424]. A wide range of weight gain, from a loss to a gain of over sixty pounds, may result in uncomplicated pregnancies, although Rosso clearly demonstrated that high weight gains do not enhance fetal growth beyond the biological limit of individual women [460]. Hytten and Leitch found weight gain during the last twenty weeks of healthy pregnancies to approach a normal distribution with a mean of 9.3 kg (20.8 pounds) [5,256].

Table 8-9
EFFECT OF MATERNAL WEIGHT GAIN ON BIRTHS
OF LOW WEIGHT FROM UNDERWEIGHT WOMEN [535]

<i>Weight gain by 12-16 weeks of gestation</i>	<i>Weight gain from first visit to 24-26 weeks</i>	<i>Number over 5% below standard</i>	<i>Low birth weight (per cent)</i>
At least average	At least average	93	5 (5.4) —
At least average	Below average or loss	30	4 (13.33) —
Less than average or a loss	At least average	52	6 (11.38) —
Less than average or a loss	Less than or a loss	45	11 (24.44) —

= 7.3%

= 17.5%

Table 8-10 shows women more than 5 per cent under standard weight at conception had low birth weight infants according to the weight gain achieved by 24-26 weeks of gestation. When the interval gain was below average, low birth weight occurred more than 2.5 times as often (20.0 per cent versus 7.59 per cent). It is apparent from the table that weight gain has more influence on the prevalence of low birth weight than prepregnancy weight.

Lowe analyzed the relationship between birth weight and weight gain in approximately 8,000 single live births, 37-44 weeks gestation, at a large hospital, 1964-67 [340]. The correlation between birth weight and maternal weight gain was 0.94. His data show, for term and near term births, the probability that birth weight is not related to maternal weight gain is infinitesimally small. Prepregnancy weight accounted for 37 per cent of the relation between birth weight and weight gain; 51 per cent was accounted for after prepregnancy weight was removed as a variable.

Table 8-10
RELEVANCE OF PREGRAVID WEIGHT AND PREGNANCY
WEIGHT GAIN TO FREQUENCY OF LOW BIRTH WEIGHT [535]

<i>Pregavid weight relative to standard weight</i>	<i>Weight gain from first visit to 24-26 weeks</i>	<i>Number of women</i>	<i>Low birth weight (percentage)</i>
Between 5% under and 25% above	At least average	190	5 (2.63)
	Less than average	192	17 (8.85)
More than 5% under	At least average	145	11 (7.59)
	Less than average	75	15 (20.0)

Lowe noted the relation between weight gain and birth weight is not continuous [340]. Further maternal weight gain has no effect at and beyond approximately 3,500 g birth weight. This is almost exactly what Rosso determined a decade later [460]. Lowe also concluded that even greater prepregnancy weight would not promote further increase in birth weight. Hence, there is a *woman specific biological maximum* of birth weight. This abstract birth weight, likely the optimal weight except in cases of overt or latent diabetes and less common medical conditions, is extremely unlikely to be achieved unless the mother is adequately nourished throughout gestation.

As Lowe's and other studies [387,424,460,462] suggest, birth weight is abnormally low if the mother gains inadequate weight during pregnancy or is underweight at the time of conception, and, especially, when both factors are present. The findings of the Collaborative Study [229,402], Tompkins and Wiehl [534,535], Lowe [340], and others all indicate that weight gain during pregnancy is a more accurate predictor of birth weight than prepregnancy weight. These studies indirectly confirm the results of numerous others, some discussed earlier, in establishing the profound effects of

maternal nutrition on birth weight. Higgins, studying 1,736 pregnancies, also showed weight gain to relate significantly to birth weight [242,431]. The average birth weight was 3,489 g for 237 women gaining the most weight during pregnancy. This was 538 grams more than the average birth weight of 100 women gaining the least. Singer et al., utilizing a subset of over 10,000 births from the Collaborative Study, analyzed the association between weight gain and infant development [500]. The mother lost weight during pregnancy in 1.9 per cent of these cases, but, unfortunately, these were excluded from the analysis. The study confirmed age, parity, and many other factors were not related to birth weight when maternal weight gain is one of the independent variables. The association between weight gain and low birth weight, as portrayed in Table 8-11, is significant at $p = 0.001$.

Table 8-11
CORRELATION BETWEEN WEIGHT GAIN DURING
PREGNANCY AND LOW BIRTH WEIGHT [500]

<i>Weight gain (kg)</i>	<i>Percentage low birth weight</i>
Loss	17.0
0-6.7 (0-15 pounds)	15.8
6.8-11.2 (16-25 pounds)	8.2
11.3-15.6 (25.3-35 pounds)	4.3
>15.6 (≥ 36 pounds)	3.0

The data in Table 8-12 reflect the relationship between weight gain, infant size, and neurological function at one year of age and mental and motor function at eight months of age. However, the degree to which the data demonstrate the association between weight gain and childhood or subsequent neurological function cannot be estimated since, as previously mentioned, the exams used are not predictive. Nevertheless, all infant abnormalities except those measured by the neurological exam were significantly related to weight gain. Interestingly, when the relationship between birth weight and infant abnormalities was removed from the analysis, low maternal weight gain remained associated with infant abnormalities.

The results in Table 8-12 varied further when actual birth weight was accounted from within the range of low birth weight infants. Maternal weight gain was not associated with later infant size or development when birth weight was between 1,001 and 1,500 g. Among infants with birth weight between 1,501 and 2,000 g, there was a significant relationship between maternal weight gain and results of both the mental and motor exams ($p < 0.05$). For birth weight between 2,001 and 2,500 g, maternal weight gain

Table 8-12

PREVALENCE OF ABNORMAL INFANT GROWTH AND DEVELOPMENT
ON LOW BIRTH WEIGHT INFANTS BY MATERNAL WEIGHT GAIN [500]

	<i>Maternal weight gain (kg)</i>			
	0-6.7	6.8-11.2	11.3-15.6	>15.6
Infant weight	15.8%	11.2%	8.4%	6.2%
Motor exam	11.3	8.0	6.8	5.2
Mental exam	12.5	9.3	8.3	7.5
Infant height	10.1	7.5	6.5	7.3
Neurologic test	8.8	7.5	7.9	7.1
Total abnormal	58.5%	43.5%	37.9%	33.3%

was associated with child weight at age one year ($p<0.05$). Motor function ($p<0.05$) and child weight ($p<0.001$) were significantly related to maternal weight gain for infants not underweight at birth.

As the length of gestation increased, the prevalence of low birth weight, in general, decreased. Birth weight was highly associated with maternal weight gain, even when the effect of weight gain on length of gestation was removed, except for pregnancies of 28-30 weeks gestation ($p<0.001$). Hence, the relationship between birth weight and weight gain is stronger than between length of gestation and weight gain. Moreover, length of gestation did not account for much of the maternal weight gain to birth weight association. Low birth weight accounted for 9.6 per cent of births over 37 weeks gestational age among women gaining less than 7.1 kilograms and 2.5 per cent among those gaining more than 15.6 kg. For births 34-36 weeks gestation, the corresponding prevalence of low birth weight were 36.6 per cent and 0.2 per cent respectively. Among underweight infants, there was no relationship which was statistically significant between gestation and maternal weight gain for each 500 g increment in birth weight.

Prepregnancy weight and weight gain were found to be somewhat negatively correlated. Hence, the relationship between weight gain and birth weight is rather more independent of prepregnancy weight than not (see beginning of this section).

There is a limit to the value of efforts to correlate maternal weights, before, during, and after pregnancy, with fetal growth, namely the role of the *ob* gene, more precisely the human homologue of the recently cloned murine gene [578]. The cellular product is leptin, a 16-kilo Dalton (kDa) peptide, which is released by fetal fat cells [499]. Placental leptin is overexpressed in diabetic pregnancies, up to 3-5 times normal during insulin treatment [318]. Leptin deficient *ob/ob* mice lack bioactive leptin and are obese but reduce their food intake when

injected with leptin. In contrast, obese humans have high plasma leptin with intact leptin receptors [109]. Obese children have high plasma leptin levels, especially girls, both with possible hypothalamic resistance to leptin [232].

There is a direct relationship between leptin level in cord blood and birth weight [501], actually one which is roughly exponential from limited data sets, perhaps reflecting the cumulative effects of leptin, similar to those of insulinlike-growth factor I (p. 112) [245,327]. The cord blood plasma level for term birth but small for gestational age infants is little more than the level in preterm but appropriate size infants [501]. Thus, it would appear the role of leptin in fetal weight gain, irrespective of these external parameters, is important. It may well be further that efforts will reveal more concerning the role of leptin in fetal growth and maternal adaptation to the pregnant state.

OUTCOME MEASURES IN THE MOTHERWELL PROTOCOL

Chapter 4 summarized the concept behind and the methods used in the long-running Motherwell pregnancy nutrition project in western Scotland. The nutritional status of pregnant women within the protocol was different at the time and remains so in retrospect. This section examines perinatal outcome in comparison to other parts of Scotland.

Table 8-13 compares inpatient perinatal deaths in Motherwell, three other Scottish reporting districts, and Scotland at large for the year 1971. Lethal anomalies and previables (<20 weeks gestation even if born alive) have been excluded, but twins and other multiple births have been included.

Table 8-13
OUTCOME OF PREGNANCY: 1971 SCOTTISH HOSPITAL
INPATIENTS (PERCENTAGES IN PARENTHESES)

Hospital/ area	Total births	Surviving live births	Perinatal deaths		
			Still- births	Neonatal deaths	Perinatal total
Aberdeen	4711	4640 (98.49)	65 (1.4)	6 (0.13)	71 (1.51)
Forth Park	1798	1754 (97.55)	24 (1.3)	20 (1.1)	44 (2.45)
Bellshill	4696	4518 (96.21)	99 (2.1)	71 (1.5)	167 (3.56)
Motherwell	994	979 (98.49)	10 (1.0)	5 (0.5)	15 (1.51)
Scotland	66420	64870 (97.67)	918 (1.4)	632 (0.95)	1550 (2.33)

By these measures, the Motherwell Protocol matched the university hospital setting in Aberdeen (see Chapter 4) in overall perinatal mortality and did better than the two other regions and Scotland as a whole. The allocation generally between stillbirths and neonatal deaths differs for Aberdeen, which may be attributed in part to a neonatal intensive care unit not available elsewhere. Neonatal deaths in both Forth Park and Bellshill exceeded the Scottish average in 1971.

The Motherwell experience, thanks to Kerr Grieve's record system, can be viewed in the further light of diet success, as defined in the Motherwell Protocol. Table 8-14 provides the cumulative perinatal outcome for the full term of the nutrition project, 1960-1976.

Table 8-14
PERINATAL DEATHS, MOTHERWELL PROTOCOL,
1960-1976, BY DIET SUCCESS GROUP

Diet category	Total births	Perinatal deaths
High	7565	115 (1.52%)
Medium	2136	67 (3.14%)
Low	5080	190 (3.74%)
Very low	909	87 (9.57%)
Total	15690	459 (2.93%)

$\chi^2 = 301.81$. d.f. = 3, p <<0.0001

The observation that the high diet success group accounted for 48.22 per cent of the whole emphasizes the achievement; the rate of perinatal death in high diet success is just under half that of the next lowest, those from medium diet success. The favorable influence on the result by a very good outcome for almost half the cases is supported further at the other end of the scale by a small group of pregnancies excluded from the table. The records for 65 mothers were incomplete, the gestational index in particular. They were mostly unbooked cases. The 65 pregnancies resulted in 11 perinatal deaths, a rate of 16.92 per cent, nearly six times the composite average of all four diet groups. The data in Table 8-14 are raw figures, with no correction for previability or lethal anomaly.

Thus, it is appropriate to say, once again, the Motherwell Protocol is a challenge to (1) past and prevailing attitudes which come from the medicalization of pregnancy relatively untutored in nutritional principles, and (2) the subtext of this book, something we will call, for present purposes, the biologic imperative of pregnancy nutrition. Since Grieve's results were on a par with the best obstetrical and neonatal units of the time in Scotland, the

other distinguishing feature of the Motherwell Protocol, the low section rate, requires examination (Table 8-15).

Table 8-15
SECTION DELIVERY AND PERINATAL DEATHS: 1972*

<i>Maternity hospital</i>	<i>Total births</i>	<i>Sections</i>	<i>Perinatal deaths</i>
Aberdeen City	2445	176 (7.20%)	44 (1.80%)
Airdrie-Coatbridge	1819	133 (7.31%)	44 (2.42%)
Dumfries	375	27 (7.20%)	5 (1.33%)
Dundee	2563	237 (9.25%)	61 (2.38%)
Dunferline-Kirkaldy	900	42 (4.67%)	28 (3.11%)
Inverness	529	36 (6.81%)	8 (1.51%)
Perth	597	21 (3.52%)	8 (1.34%)
Subtotal	9228	672 (7.28%)	198 (2.15%)
Scotland at large	62533	4462 (7.14%)	1452 (2.32%)
Motherwell-Wishaw	980	13 (1.33%)	16 (1.63%)

*Year selected because of ready availability of comparative information.

The section rate in Motherwell-Wishaw for 1972 was only 18.63 per cent of the whole of Scotland and 18.27 per cent of the average of obstetrical units in other communities, differing in demographic attributes. In 1972, Aberdeen was mainly a university town, becoming industrialized following the discovery of North Sea oil fields. Dundee was of similar size, already industrial and a major port, but the more modern university hospital (Ninewells) was still two years in the future. The remainder are small cities and towns from many parts of Scotland. Airdrie-Coatbridge is an industrial center just north of the Motherwell-Wishaw area, due east of Glasgow. Perth is an access city for the highlands, west of Dundee. Dumfries is in southern Scotland, near the border with England, while Inverness is the principal city of northern Scotland, at the head of Loch Ness. Dunferline and Kirkaldy are small towns near Edinburgh but north of the Firth of Forth.

Motherwell and Wishaw are industrial cities in the shadow of Glasgow with its historic tradition of shipbuilding along the River Clyde, one of the great world concentrations of the force of the industrial revolution.

The well-documented comparative results: excellent neonatal outcome with minimal intervention by section delivery, but using a high protein, calorie restricted pregnancy diet, while a challenge to the concept of an efficient biologic imperative, do offer a way to reconcile the seemingly irreconcilable corners of the problems and claims for nutrition before, during, and after human gestation. This will be taken up specifically in the

final chapter.

The greater diversity of ethnic and racial factors in the United States has served, in part, to confound analysis of pregnancy outcome. For example, James reported from the national database for 1983-84 that, despite apparently similar socioeconomic profiles, infant mortality among Mexican-Americans was just 8/1000 live births, less than half the rate for African-Americans at 18/1000 live births [262]. In fact, infant mortality was the same among Mexican Americans as for non-Hispanic whites. Low birth weight followed a similar pattern. Table 8-16 has been recalculated from the data of James [262].

Table 8-16
ETHNIC-RACIAL RATES OF LOW BIRTH WEIGHT,
UNITED STATES, 1983-1984 [262]

	<i>Live births</i>	<i>Low birth weight</i>	<i>Per cent</i>
Non-Hispanic			
Black	1,083,718	124,628	11.5
White	5,097,581	239,586	4.7
Total Hispanic	561,107	29,994	5.3
Cuban	21,943	1,053	4.8
Mexican	455,104	22,300	4.9
Puerto Rican	84,060	6,641	7.9

James noted: "In the case of African Americans, we have a racial minority group that has been thwarted in almost every conceivable way by a larger society in its efforts to develop cultural as well as economic strengths. In light of this, the heightened vulnerability of African Americans to a host of obviously preventable health problems should surprise no one [262]."

An earlier report compared birth weight outcomes according to assessed adequacy of prenatal care [497]. This was based on the combination of two factors: (1) the gestational week for the first prenatal visit, and (2) the total number of visits. When the criteria were put into effect, a favorable result was seen for all categories (Table 8-17) [497]. All of these mean birth weights are in "good outcome" territory but the relative effect is within a fairly narrow range. Stickle and Ma, examining 130,000 births, found that starting prenatal care in the first trimester had the best outcome [513].

These are specific time frames with antecedent conditions which are not readily matched elsewhere. Williams and Chen found the principles behind the then concurrent (1977) noteworthy decline in perinatal mortality rates in California [563]. A strong secular trend from 1960 to 1977 revealed decreases

Table 8-17
BIRTH WEIGHT DIFFERENTIAL ACCORDING
TO ADEQUACY OF PRENATAL CARE [497]

	<i>Adequate care</i>	<i>Inadequate care</i>	<i>Difference</i>
White	3481	3294	-187
Black	3226	3005	-221
Mexican	3435	3295	-140
Other	3331	3184	-147
Total	3419	3206	-213

in the weight specific mortality rate accounted for 81 per cent of overall improvement and only 19 per cent could be attributed to an upward change in birth weights *per se*, another example of the impact of interventional obstetrics and neonatology as noted in the prior discussion on WIC (Chapter 6) [407,526]. The trend was accompanied by a rise in use of section delivery from 4.8 per cent in 1960 to 15.0 per cent in 1977. Greater increases were seen for some of the low birth weight categories (Table 8-18) [563]. The right-hand column has been added to indicate relative increase in use of section delivery.

Table 8-18
ESTIMATED INCREASE IN SECTION DELIVERY RATES
FOR SINGLETON BIRTHS, CALIFORNIA, 1960-1977 [563]

<i>Birth weight</i>	<i>Section rates (per cent)</i>		<i>Ratio</i> <i>1977/1960</i>
	<i>1960</i>	<i>1977</i>	
501-1000 g	3.6	11.7	3.25
1001-1500	7.8	24.6	3.15
1501-2000	10.4	25.8	2.48
2001-2500	8.2	19.3	2.35
2501-3000	5.4	19.5	3.61
3001-3500	4.4	13.5	3.07
3501-4000	4.0	14.8	3.70
4001-4500	4.8	17.8	3.71
>4500	6.6	24.8	3.76
Total	4.8	15.0	3.12

By the mid-1970s perinatal mortality for birth weights between 1,501-2,000 grams in section-delivered cases had fallen below that for vaginal delivery. The overall perinatal mortality was reported in detail; the summary for births between 2,501 and 4,500 grams for 1978, the first year after the 18-year

survey, was 2.1 per thousand. The perinatal mortality rate for section deliveries was 3.4 per cent; the postvaginal rate was 1.8 per thousand [563]. Cocaine can precipitate diabetic ketoacidosis [553]. It has teratogenic effects [546], a higher risk over many doses [540], and poses interpretative problems when other factors are present [305]. Fortunately, attention is once again becoming focused on effects of prenatal drug exposure on early postnatal development [165].

Finally, the effects of extensive dermal burns in pregnancy deserve comment [128,261,522]. Jain and Garg reviewed 25 cases during a six-year period (1986-1991) [261]. A total of 1260 individuals were admitted to the burn unit at the JLN Hospital, Bhilai (MP), India. There were 187 women of child-bearing age with burns from 15 to 100 per cent of total body surface area (TBSA). Twenty-five of the women were pregnant. Sixteen had normal, full-term deliveries; there were nine miscarriages or fetal deaths and five maternal deaths (20.0 per cent) (Table 8-19).

Table 8-19
EXTENT OF BURNS AND MATERNAL OUTCOME
AS PER CENT OF BODY SURFACE AREA [261]

BSA (%)	Patients (#)	Survived (#)	Maternal deaths
15-30	7	7	0
31-49	8	8	0
50-65	8	5	3
66-89	0	0	0
95-100	2	0	2

Miscarriage or fetal death occurred in all three trimesters (Table 8-20). These papers made no special mention of nutritional needs of pregnancy within the intensive care that large burns require.

Table 8-20
DURATION OF PREGNANCY AND OUTCOME [261]

Stage of pregnancy	Patients	Fetal death	Maternal death after fetal death*
1st trimester	6	4	0
2nd trimester	12	4	2
3rd trimester	7	1	1

*The trimester of the other two maternal deaths was not given.

Chapter 9

NUTRITION DURING INFANCY AND EARLY CHILDHOOD

MALNUTRITION DURING THE earliest stages of postnatal life causes stunting of physical growth and often leads to irreversible mental and emotional impairment by retarding maturation and growth of individual cells of the central nervous system [160].

Undernutrition during infancy or early childhood can depress the metabolic conversion of phenylalanine to tyrosine, changing the phenylalanine:tyrosine ratio in the blood [160]. This metabolic disorder, accompanied by defective enzymatic function, can lead to nonclassical or transient phenylketonuria (PKU), with a risk for mental retardation, but less so than the genetic form of the disorder [376,436].

A deficiency during infancy of an enzyme similar in function and structure to vitamin B₆ can lead to hyperirritability, abnormal development, and behavioral disorders [160]. While isolated deficiencies of such factors are unlikely, multiple limited intakes may have additive effects.

Mental development is directly related to infant and childhood nutrition. Birch and Gussow stated that sound nutrition during infancy and early childhood is of paramount importance [39]. They believed that nutrition is the most important factor in determining a child's growth, mental and physical functioning, and resistance to disease. They demonstrated that among many persons who experience educational failure, improvement cannot be accomplished without concomitant improvements in nutrition and health care. This is especially so when language retardation is considered, since malnutrition is a critical negative factor which cuts across national, cultural, and racial lines [27,86,91,94,383].

The unequivocal dependence of education on nutrition has been

recognized by many educators. The long-time president of Boston University, John Silber, profoundly stated in 1975:

The highest priority in American education today should be the establishment of a national program of nutrition and early childhood education . . . We must . . . prevent the occurrence of gratuitous retardation, that is, of retardation that results, not from genetic malformation or other unavoidable causes, but rather from social neglect. In order to do this, we must understand the importance of nutrition, especially the nutrition of the fetus . . . It is a gratuitous retardation, imposed on those children whose prenatal and early nutrition has been defective. Only a society that has lost its respect for human life and its concern for the fulfillment of each individual can be indifferent to this retardation. If we are to avoid such retardation, we must insure that no mother, either through poverty or ignorance, malnourishes her children in utero. [498]

Independent of (but sometimes derived from) poor gestational nutrition, severe malnutrition during infancy may cause impairment of intellectual functions [83]. Thirty-six children aged seven to 14 years were given IQ tests. All were severely malnourished between four and 24 months of age. None tested above normal (Table 9-1).

Table 9-1
DISTRIBUTION OF IQ AT 7-14 YEARS IN CHILDREN SEVERELY
MALNOURISHED BETWEEN 4 AND 24 MONTHS POSTNATAL [83]

<i>IQ range</i>	<i>Percentage distribution of IQ</i>		
	<i>Number of children</i>	<i>Per cent</i>	<i>Per cent IQ for normal children</i>
<70	1	2.77	2.1
71-90	17	47.22	19.3
91-110	18	50.00	46.4
111-130	0	0.00	26.1
131-150	0	0.00	5.8

Numbers do not total to 100 per cent due to rounding.

The obvious shift in distribution is downwards from IQ ratings of 111-130 into the next two lower ranks. A normative distribution for a sample of 36 would approximate this: >130, 1 case; 111-130, 9 cases; 91-110, 17 cases; 71-90, 8 cases; and <70, 1 case. The difference between the percentage of the 36 malnourished children with subnormal intelligence and the expected rate from an unbiased population is significant at the 1 percent level.

RETROSPECTIVE NUTRITIONAL STUDIES

A wealth of studies have shown mental development is directly related to infant and childhood nutrition. Stoch and Smythe set up a child nutritional study at the University of Cape Town, South Africa [514]. There were 21 survivors of 24 severely malnourished infants matched by age and sex with another 21 infants, also small for age, presumably better nourished. The 21 study infants were below the 2.5th percentile for weight for their age, an extreme deviation from the median. Controls, from families with closely similar standards of living, were, on the average, at or below the tenth percentile for weight for their age. It is important to keep in mind both samples were at the lowest end of weight distribution. Viewed from one perspective, the index study group would be matched *statistically* with the lowest quartile of the control group. Although the parents of the controls as well as the index cases were classified in the lowest economic group, unskilled laborers with minimal incomes, the control children tended to come from larger families with slightly higher incomes and parents with slightly better educational achievements. Accordingly, one might say the index group were in the lowest segment of the mutually bottom rank. Stoch and Smythe gave no further particulars on the point [514].

It is noteworthy there were no major differences in either IQ or head circumference between the parents of the two groups of infants. The head circumferences of the index cases were generally well below the mean for American children, whereas the control group measurements fit well into the lower half of the normal American range. This is in agreement with the findings in the WIC study (p. 146) but is actually a better data set because it is over a longer period of time. The markedly underweight children were examined about one year old and then at six to twelve month intervals. This was, then, a long-term longitudinal study with a coherent result.

Although the maternal nutritional intake for either group was not assessed, it is highly probable the mothers of the study group were more undernourished than mothers of the controls. A further limitation of the study was a failure to include birth weight data. In addition to head circumference, physical and intellectual development were evaluated at one year of age and every six months thereafter up to seven years. At all ages, the malnourished children had smaller head circumferences and scored lower on the IQ tests. The study group infants were also shorter and weighed less. For all measurements and IQ scores, differences were significant at 1 percent. The average IQ of the study group was 70 in contrast to a mean score of 93 among controls.

As the children got older, the differences in height and head circumference remained the same, indicating permanent pernicious effects of the

poor nutrition. The difference in weight became less marked, although study group infants still weighed less, on average, than controls.

Many other studies have demonstrated that malnutrition during infancy or early childhood impairs cognitive function and retards physical growth. The British Medical Research Council extensively studied the consequences of severe malnutrition in Jamaica [240]. IQ tests were given to 71 boys hospitalized during the first two years of life due to malnutrition. During the study ages ranged from six to ten years. Table 9-2 shows the IQ scores of the study infants along with 38 siblings nearest in age to each study infant, plus 71 other controls. The controls were matched with study children for sex and somewhat for age and socioeconomic status but not for other factors.

As shown in the table, the greatest differences in IQ scores were between the malnourished and control groups, emphasizing the pernicious effects of malnutrition. The smallest differences in IQs were between siblings of the malnourished children and the controls.

Table 9-2
SCORES ON INTELLIGENCE EXAMS, MALNOURISHED INFANTS,
NEAREST AGE SIBLINGS, AND CONTROLS, IN JAMAICA [240]

	<i>Index children</i>	<i>Close siblings</i>	<i>Unrelated controls</i>	<i>Significance level</i>		
				<i>Index vs. siblings</i>	<i>Index vs. controls</i>	<i>Siblings vs. controls</i>
Number	71	38	71			
Full scale IQ	57.72	61.84	65.09	0.025	0.005	NS
Performance IQ	56.30	58.03	63.69	NS	0.005	0.05
Verbal IQ	64.92	71.03	73.70	0.005	0.005	NS

NS = not significant

Liang et al. compared the IQ scores of 12 children poorly nourished during their first six years postnatal and of 19 children with clinical signs of vitamin A deficiency for two to four years to those of 33 reasonably healthy children who had no signs of malnutrition during their first six years [325]. All 64 children resided in Bogor, Indonesia, and were tested between their 6th and 13th birthdays. Except for socioeconomic status, the study was not well controlled.

Mental retardation was considerably more common in the 19 index children with vitamin A deficiency. These children probably also had deficiencies of other nutrients. As expected, the 33 never malnourished children had the highest IQ scores. Scores on the Goodenough IQ exam (which involved the drawing, without regard to artistic ability, a human

figure) were significantly lower among the 31 children from both groups than among the 33 well-nourished children ($p<0.01$).

A study of two-year-old malnourished children identified an average increase of 18 points in IQ after diets were dramatically improved [299]. Dietary intervention did not result in an increase in IQ after the children reached four years of age. This is consistent with the virtual cessation of brain development at four years [139,514].

Cravioto and Robles showed that physical growth was stunted and Developmental Quotients (DQs) were abnormally low among 20 infants and children suffering from third degree protein calorie malnutrition [115]. At the time of examinations, six infants were less than six months old (designated as Subgroup A in Table 9-3), nine children were between 15 and 29 months of age (Subgroup B), and the remaining five were between 37 and 42 months old (Subgroup C). The validity of the results of the study is diminished by the lack of controls and the seemingly improper (although probably consistent) administration of the Gesell examinations.

They found the earlier in life the children were malnourished, the more permanent was resulting mental and physical impairment. As the children recovered from malnutrition, the DQs increased for the children in Subgroups B and C, but not among the six infants of Subgroup A [115]. Their findings were confirmed by Birch and Gussow, who demonstrated that mental retardation persists among children who had been severely malnourished early in life, regardless of subsequent nutrition and other environmental factors [39]. Hence, severe malnutrition during the early stages of life can result in irreversible neurological underdevelopment or brain damage. The effects are less divergent in adolescence [189].

Table 9-3
DEVELOPMENTAL QUOTIENTS (GESELL) IN 20 CHILDREN PRIOR
TO TREATMENT FOR SEVERE PROTEIN CALORIE MALNUTRITION [115]

Group	Postnatal age in months	Field of behavior			
		Motor	Adaptive	Language	Personal-Social
A	3-6 Mean = 4.8	33	40	33	27
B	15-29 Mean = 23	48	45	36	42
C	37-42 Mean = 39	34	34	33	37

EFFECT OF MALNUTRITION ON LACTATION

Maternal nutrition has a profound effect on the quantity [11,124,263,303] and possibly on the quality of breast milk [134,263,332]. There may be a deficiency of various nutrients in the milk produced by undernourished mothers [39], especially the protein content [125,263,332,558], whereas changes in diet within a reasonably normal range have little or no effect on milk content [217,558]. It has been known for more than a century that malnutrition can retard lactation. An 1871 study showed that 16 of 43 malnourished lactating mothers produced very little milk; this was during the siege of Paris in the midst of the Franco-Prussian War of 1870-71 [126]. There was widespread lactational failure during the much longer siege of Leningrad in World War II [11]. Nevertheless, sound prenatal nutrition is essential for proper nourishment of breast-fed infants. In one sense, additional weight gain during pregnancy is preparatory for lactation, and inadequate gain will harm this function. Average weight gain in pregnancy, with a healthy outcome for the fetus, includes about 4 kg of maternal fat deposition or 36,000 kcal [527]. High fat content human milk may have as much as 8 g/100 ml (Table 9-5). At this level, assuming no further fat intake or manufacture from other food substrates, the entire 4 kg will be used up by day 17 of the third postnatal month!

An interventional program in India gave nutritional support during the third trimester [199] in preparation for lactation. Little difference was seen in the first month, but in the third month, the supplemented mothers produced a mean of 465 grams of milk against 158 grams for those without the supplements.

Good pregnancy outcome was defined by Abrams and Parker [5] as: (1) vaginal birth between 37 and 42 weeks gestation; (2) a living, singleton infant of appropriate weight for age and no anomalies; and (3) a mother with no signs of gestational diabetes or hypertensive disease including gestosis. Abrams and Parker have emphasized this outcome is associated with a much wider range of total maternal weight gain than previously or currently recommended (1990). They found the range of gain at 12-18 kg described 50 per cent of 4,674 women during the years 1980-88; a gain of 10-21 kg covered 80 per cent of the cohort. Mean weight gain correlated with pre-pregnancy body mass, parity, race, and especially so with overweight status and overt obesity, but not with age or smoking status. The mean weight gain for 4,674 pregnant women was 15.04 ± 0.07 kg (standard deviation = 4.96 kg). Hytten and Leitch came to the same conclusion [256]: "Perhaps the most astonishing finding about weight gain in pregnancy is the range that is compatible with clinical normality in pregnancy and a normal outcome."

While the specificity of human milk for human infants has been reaffirmed [267], there is variation in content. Table 9-4 compares human milk content to cow milk and Table 9-5 displays the variability of human milk.

Table 9-4
COMPOSITION OF MATURE HUMAN MILK
AND COW MILK [ADAPTED FROM 218]

<i>Component</i>	<i>Human milk</i>	<i>Cow milk</i>
Water, 100 ml (dl)	87.1	87.3
Energy, kcal/dl	75	69
Total solids, g/dl	12.9	12.7
Protein	1.1	3.3
Fat	4.5	3.7
Lactose	6.8	4.8
Ash	0.21	0.72
Proteins, % of total		
Casein	40	82
Whey	60	18
Calcium, mg/liter	340	1250
Phosphorus, mg/liter	140	960
Vitamins, per liter		
Vitamin A, IU	1898	1025
Thiamine (B ₁), µg	160	440
Riboflavin (B ₂), µg	360	1750
Niacin (B ₃), µg	1470	940
Ascorbic acid, mg (Vitamin C)	43	11

Human milk, and especially banked human milk, is not the constant mix of ingredients as is the design for standardized formulas [122,192].

In 1945, Dieckmann et al. published on diet regulation [134] prefatory to the more detailed analysis of the effects of enhanced protein intake on human gestation and the newborn [135,136]; in this paper, he made the assertion "... the quality of human milk has been shown to be affected by a deficient diet . . ." without any data to substantiate the claim.

A number of papers and reports in the 1970s expanded general knowledge and appreciation of the physiology, value, and techniques of lactation [12,164,268,558]. A more recent and succinct review on breast feeding, unfortunately without instructional pictures or diagrams, is that of Schulman and Rosner [477].

Nichols and Nichols [400] defined nutrient adequacy as the physiologic state in which supplementary nutrient intake is *not* associated with any

Table 9-5

VARIATION IN COMPOSITION OF MATURE HUMAN MILK (PER 100 ML) [349]

Component	Minimum	Maximum
Energy (kcal)	45.0	119.0
Protein (g)	0.7	2.0
Fat (g)	1.3	8.3
Carbohydrate (g)	5.0	9.2
Calcium (mg)	17.0	61.0
Phosphorus (mg)	7.0	27.0
Sodium (mg)	6.0	44.0
Potassium (mg)	37.0	64.0
Chloride (mg)	9.0	73.0

increase in body stores as measured by nutrient concentration or by *nutrient mediated functions*. They considered the latter to be more important. This principle applies to lactation as much as it does to transplacental fetal nourishment.

Widdowson summarized the nutritive and energy cost of lactation, pointing out it includes the energy cost of milk components as such plus that required to synthesize the lactose, proteins, and fat from maternally ingested substrates [558]. Table 9-6 lists the changes in energy cost as an infant matures from birth to six months of age.

Table 9-6
ENERGY COST OF LACTATION FOR FIRST
SIX MONTHS POST NATAL LIFE [558]

Age of infant (months)	Volume of milk taken (ml/day)	Energy value of milk (kcal)	Total energy cost of milk production at 90% efficiency* (kcal/day)
0-1	600	402	446
1-2	840	563	626
2-3	930	623	692
3-4	960	643	714
4-5	1010	677	752
5-6	1100	737	819

*Based on the calculations by Thomson, Hytten, and Billewicz [528].

The issues of lactation pertain directly to nourishing the infant born prematurely [195]. Usually, pregnancy preparation for lactation is complete mainly by the last few weeks, or roughly from the 38th week onward [441] and this does not augur well for very preterm infants at the lowest birth

weights. The endocrine profiles in human gestation are supportive of this maturational scale, a cumulative effect of their actions on the various tissues. Human placental lactogen, which is also known as human chorionic somatomammotropin, is detected at steadily increasing levels until about 36 weeks, after which the rise is much slower, perhaps even on a plateau; this tracks placental mass very closely, actually leading the way by a six-week interval, after 10-11 weeks menstrual age [226,481]. It would be tempting to attribute placental growth to the autotrophic action of hPL were it not for seemingly well established observations of successful pregnancy in the absence of hPL [401,499]. The applicability of the case by Nielsen [401] in this situation is doubtful. The woman had fairly high prednisone treatment for sarcoidosis (60 mg per day) until the 16th week of gestation.

There is a strong correlation between placental lactogen (hPL) levels and fetal weight which persists after glucose related variables are accounted for [306]; this is interesting in light of the low levels of hPL in fetal blood [226]. There are *high affinity* hPL receptors in fetal liver [182,183], suggesting rapid clearance and a possible stimulatory role for hPL in fetal hepatic protein synthesis. How one is to explain the anti-insulin effects, decreased gluconeogenesis, increased lipolysis, and ketogenesis in pregnancy [198], thought to be due to the activity of placental lactogen, in the genetic absence of the same, is a question for future research.

An important question is whether human lactation can compensate for the evident deprivation of preterm birth and low birth weight. The more immature or smaller the infant, the greater the likelihood that specific interventional therapy will have to be supplied. There are several other known factors of importance. A useful introduction to this problem, with some specific but limited examples, is Bainbridge and Tsang [18], part of a larger work on childhood nutrition. The tone and direction of their chapter brings to mind other lists of ingredients which are *complete* as of the date of data collection or publication which seem, to this author, to always leave something out, if we only knew what.

The absorptive capacity of newborns is in part a function of their size which is directly reflected in the length of the intestinal tract. In fact, linear relationships have been demonstrated between gestational age and crown heel body length and the lengths of small, large, and entire enteric tract [486]. The birth weight had a more complex, exponential relationship. The effects of intrauterine growth retardation were examined in the 73 infants (out of 100) with gestational age ≥ 24 weeks; 21 infants fit into this category, defined as <10 th percentile for age by U.S. standards [343]. The relative lengths of the small intestine for the growth-retarded infants ranged from 0.81 to 0.91 of normal for gestational age. When these were put back into the

general scheme, however, the basic relation between bowel length, body length, and gestational age was maintained (Table 9-7) [486]. There is little information on the relation of bowel resection (as for necrotizing enterocolitis) to subsequent neurological or mental development. Valman studied child intelligence after malnutrition resulting from neonatal resection of ileum [543]. No difference was found in the outcome of the "draw a man test," although the children in both the cystic fibrosis and the ileum resection groups with the lowest scores had been in hospital the longest time.

Table 9-7
LENGTH OF HUMAN INFANTILE INTESTINE BY GESTATIONAL AGE [486]

Gestation (weeks)	Growth category	N	Birth weight (g)	Length of intestine (cm)	
				Small	Large
$\geq 24\text{-}27$	AGA	15	763 \pm 141	109 \pm 18	25 \pm 4
	IUGR	7	504 \pm 56	89 \pm 16	21 \pm 3
$\geq 28\text{-}31$	AGA	10	1115 \pm 215	138 \pm 31	31 \pm 3
	IUGR	2	915 \pm 50	117 \pm 13	26 \pm 4
$\geq 32\text{-}35$	AGA	11	1864 \pm 448	149 \pm 23	35 \pm 4
	IUGR	7	1184 \pm 188	136 \pm 22	30 \pm 5
$\geq 36\text{-}40$	AGA	16	3033 \pm 51	176 \pm 34	39 \pm 5
	IUGR	5	2028 \pm 357	149 \pm 16	34 \pm 6

Statistical limits are standard deviations (S.D.).

These are important considerations due to their contribution to maintenance of health. Immaturity of intestinal mucosal function is also a factor; for example, glucose absorption in infants up to one year of age has a limit of around 14 g/hr/cm [208]. Pelletier et al. discerned evidence for a potentiating effect of malnutrition on child mortality [417]. Mortality increases exponentially with declining weight for age. The effect is consistent across six major studies which were analyzed and summarized. No threshold effect was identified. This key paper confirms that mild to moderate morbidity is definitely associated with an increased risk for mortality [417]. This was anticipated by a much older study in Glasgow, Scotland [144].

Donnet and Stanfield studied the Blackhill area of Glasgow, well known for its state of deprivation, and compared it to Carntyne, more representative of the city at large. The infants from Blackhill were small: 19.1 per cent weighed ≤ 2500 g and 10.3 per cent were born at <37 weeks gestational age. Tanner's standards were applied [518,519]: by nine months postnatal age, 14.3 per cent were below the 3rd percentile for weight and 17.9 per cent were below the 3rd percentile for length. The small or underweight infants had more hospitalizations, 38.2 per cent with a mean of 2.0 admissions versus 9.6

per cent with a mean of 1.4 admissions [144].

Pencharz et al. studied total body protein turnover in premature neonates and the effect of birth weight, intrauterine nutritional status and diet [418]. Total body nitrogen flux is 26 per cent higher in small for gestational age infants than in appropriate for gestational age newborns; similarly, whole body protein synthesis and breakdown increase by 26 and 35 per cent respectively ($p<0.01$). Lower birth weight infants (<1500 g) have higher rates of skeletal muscle protein breakdown: 1.23 ± 1.12 g/kg/day versus 0.54 ± 0.28 g/kg/day ($p<0.05$). Premature infants have limited reserves of energy and protein. The immaturity of the gastroenteric tract is a factor here. Graded parenteral feedings indicate that energy intake has an effect on protein synthesis, for which energy is required.

Feeding premature infants only glucose without amino acids was challenged in 1977 [195]. Plasma-free amino acids in low birth weight infants were compared after oral milk and total parenteral nutrition (TPN) [243]. The "normal range" of plasma amino acids for infants of low birth weight is wider than for term infants. TPN resulted in higher values, in general, especially for aspartic acid, phenylalanine, cysteine, leucine, isoleucine, and glutamic acid, after ten days. When TPN stopped, higher values gradually fell toward the physiologic range and one month later, no difference was found. Preterm infants had especially high values of lysine (48.4 ± 16.5 $\mu\text{mol}/\text{dl}$ versus 10.27 ± 3.3 at term) [243].

Räihä and Rassin and associates presented a series of basic papers on milk protein quality and quantity for the nutritional management of preterm infants [121,123,178,190,191,435-438]. These consider several specific databases and offer commentary and interpretation. Moreover, they place the nutritional problems of preterm infants in a continuum from the intrauterine aspect. They discounted the concern of Goldman et al. on latent protein effect [204]. Breast milk has a protein content of 6.0-7.2 g/kg/day compared to formula Goldman studied, 4.7 g/kg/day.

The index paper among these reports is the commentary by Gaull et al. [192], which is critical of the emphasis on growth by weight and length using formulas. They emphasized there is a direct metabolic cost to this approach which has to be accounted: azotemia, aminoaciduria, metabolic acidosis, and some ammonemia. A pitfall in the argument from Davies and Evans is the normative reference points: primary data from Welsh infants, compared to Finnish infants, and charted on an American growth matrix [121]! The actual composition (remember the discussion is over substitutes for transplacental nutrition) has to be more precisely progressive over time and on some form of physiologic schedule.

Moderately longer-term consideration of replenishment has demonstrated

that high caloric intake occurs early in the main [108]. Lean body mass is favored when formula provide 15 per cent of calories from protein rather than 9 per cent. MacLean and Graham, studying older infants, found body mass to be related to fat deposits when they were recovering from malnourishment; maintenance of lean body mass required high protein intake of high quality [348]. There is little reason to think the same principle does not apply to many, if not most, comparable situations which would include the feeding of low birth weight infants.

The obvious nutritional and protective immunological value of human milk cannot overcome special deficiencies in maternal diet, especially if a deficit continues during active lactation. Zmora et al. reported multiple nutritional deficiencies in infants from a strict vegetarian community [580]. Four infants from a new, rather strict, vegan religious community were breast fed to age three months and then were put on low calorie density fluid preparations. All four had severe protein-calorie malnutrition, prominent rickets, osteoporosis or osteomalacia, and vitamin B₁₂ and other micronutrient deficiencies. One infant died; the others recovered without medical incident. Follow-up identified a clear continuing resistance in the colony against regular B₁₂ supplements.

EFFECT OF FOOD INTAKE ON BRAIN FUNCTION

It has been suggested the actual diet consumed influences food consumption through actions on brain function [174]. A rich carbohydrate intake leads to an increase in brain serotonin through changes in the tryptophan:neutral amino acid ratio. A rich protein intake promotes a decrease in brain serotonin. As free fatty acids are detached from albumin binding sites, more tryptophan binding is feasible. There are effects of this on behavior, including food intake. The role of this system in pregnancy deserves thorough investigation. The hypothalamus is involved in numerous vegetative functions, including feeding. Neural discharge varies according to the blood glucose level [316,404]. The satiety center is actually an interaction between the lateral hypothalamus and the ventromedial nucleus. Stimulation of the lateral hypothalamus causes an animal to eat voraciously, or *hyperphagia* [316,506]. Stimulation of the ventromedial nucleus promotes satiety, and an experimental animal will refuse to eat, even in the presence of palatable food, or *aphagia*. Destructive lesions in either locus have the opposite effect.

There are direct stimulatory roles for amino acids in the brain, specifically γ -aminobutyric acid and glycine, which act to open anion channels countering the action of acetylcholine which opens cation channels [399].

The relationship of these functions to substrate availability in developing fetuses, animal or human, has not been sufficiently examined on which to make report or comment.

Chapter 10

THE BIOLOGICAL IMPERATIVE

WRITING FIFTY-FIVE YEARS ago from the perspective of the first fifteen years of experience of Chicago Lying-in Hospital, William J. Dieckmann combined one overt recommendation with a tabular datum which together state the problem of pregnancy nutrition and its solution [134]. In retrospect, the two points encompassed much of the fault behind American obstetrical care of the 1950s, 1960s, and 1970s, and the key, undeveloped at the time, to a fundamental comprehension of the forces, powers, and needs of gestational fetal development.

Dieckmann stated:

We believe that there is no need for a total weight gain greater than 8 kilograms above the ideal weight (p. 707) . . . We are limiting the total gain above the ideal weight to a maximum of 8 kilograms by restricting the caloric content of the pregnancy diet. (p. 711)

The dietary restriction he had in mind was 1,800 kilocalories per diem. He did not define ideal weight, converting the relational scheme to one of absolute weight and intake control, away from patient specific needs.

The tabular datum was a recommendation of 88 grams of protein *per day* (his Tables V and VI). The imprimatur of Professor Dieckmann, published in the *American Journal of Obstetrics and Gynecology*, has to be viewed a major impetus for the weight control theme of pregnancy care which lasted beyond the FDA hearings on thiazide diuretics in July 1975 [584], as reflected in the statement by Chesley (who was present at the hearing) in 1978: "The current practice of nearly all American obstetricians in limiting weight gain during pregnancy to 15 or 20 pounds . . . [98, p. 32]."

The hearings confirmed various events and changes in practice which had been developing slowly over the previous 5 to 10 years. Since weight control

was obviously not enforceable by diet alone, the women eating more than they were supposed to (as was pointed out by Dieckmann later [135,136]), regulation of body water content by pharmacological means became popular in an effort to control weight gain.

In contrast to the forum of publication in 1945, Dieckmann's more constructive 1953 papers were in the *Journal of the American Dietetic Association*, a journal unlikely to be found in the consulting rooms of American obstetricians. In fact, Chesley did not cite them! This is the professional dilemma; where is the necessary information to be found? Interestingly, Dieckmann's physiological objectives were very similar to those being put into place at the time, with more stringent clinical control, by Kerr Grieve [211-213].

This book is an attempt to bring together enough of the now remarkably large, and continuously expanding, frontier of necessary knowledge. In reviewing hundreds of papers since the first edition of 1979, and a rather large number from before 1979 but not referenced then, it seems possible now to sculpt the outlines of where both research and cogent clinical observation are headed. One task the review forced this author to undertake was to recalculate all percentages, all χ^2 values, to put data into two graphics programs, to convert the literally hundreds of tabular entries published only as percentages without the basic raw data, and to seek, but not always find, the basis for inconsistent group numbers across many sets of papers from particular laboratories and clinics, and other discordancies. This endeavor was approached from two standpoints: (1) other forms of analysis, including biological credibility rather than plausibility, were more likely to be productive than statistical mechanics, and (2) coherence of the theme and information was to be valued over completeness of a data matrix. We can only deal with information obtained and published. If the design of an investigation is based on reasoning which is faulty because one or more operational assumptions are false, or subject to variation not known or considered, the task in review is to find what portion of the report or analysis retains its validity and applicability.

In this regard, the pragmatic attitude of Prentice and coworkers [425,427-430] is both commendable and correct. It is true the processes of fertilization, blastocyst formation, implantation, placental growth and differentiation, fetal growth and maturation, and intrapartum and postpartum adaptation for both mother and child are profound and complex. *But they are ordered within biological limits that can be comprehended.*

The biological imperative is the sum of the conditions and forces of fetogenesis and maternal accommodation which results in the outcome so eloquently expressed by Abrams and Parker in 1990[5], a well formed infant

of appropriate size and maturity, delivered vaginally, with a healthy mother who recovers promptly from her confinement. The past 40 years have seen a progression of interest in and active research on a wide variety of factors in cells and tissues which comprise the living organism. We might list proenzymes, the transcription of genetic factors, the redundancy of cell signalling substances, the concept of receptor activation, rate limiting steps, immune tolerance toward the fetus, maladaptations due to upregulation of functional responses, mutual hormonal inhibition, and toxic interference with natural processes.

There are many aspects of the relevant cytochemistry wherein self-assembly is important and many morphogenetic processes which are self-organizing. One point for analysis is determining what these factors are and what conditions are required for self assembly or self organization to occur.

None of the basic functions of living tissues from this partial list is shut down completely just because a woman is pregnant. In other words, the most complex mammalian biological function, gestation, *is itself a biological function* with an impact in every nook and cranny of the pregnant woman and in all aspects of fetal growth and development. There is a moving homeostasis of pregnancy which we can interrupt all too easily when we apply actions or remedies only empirically. To restate the biological imperative therapeutically or preventively requires extraordinary knowledge of that homeostasis. This is a complex situation with many potentially confounding factors [305]. We are not there yet, but we are much closer than we were 20 years ago. One important way the ultimate goal of awareness has come into focus is to appreciate that discoveries and insights into human cellular biology are quite properly subjects for particular assessment in pregnancy. There will be many blind alleys, but the investigational journey must proceed. The work on pregnancy nutrition of the past century is one corner of the map, what surveyors call the point of origin. The next sections are preliminary sketches of some of the factors to consider, by which we might obtain closure.

J.W.B. Douglas, in 1950, surveyed factors in Great Britain associated with prematurity [146], finding a significantly low "incidence" of premature birth only in the most prosperous 9 *per cent* of the population. He accessed records on 13,257 singleton births, from a single week in March 1946, using the standard birth weight criterion for prematures, <2,500 g. In line with British tradition, Douglas classified women by social class. The special value of a long paper is that he went further. Graded differences were found in the highest socioeconomic class for prematurity by maternal age (Table 10-1).

There was little difference for older (≥ 26 years) first births in women of the highest social class and all of the wives of manual workers. Douglas reported a χ^2 of 6.24, $p < 0.02$ using the break point of 2,945 grams. From his numbers,

the actual p value was 0.0125. Reevaluation of the data from 21-25 year olds yields a $\chi^2 = 6.5045$, $p = 0.0108$ (1 degree of freedom for both calculations).

A comparable examination of the distribution of birth weights for second or more births is in Table 10-1 as bold numbers, the lower line for each age range and social group.

Table 10-1
BIRTH WEIGHTS UNDER 2500 GRAMS BY SOCIAL CLASS,
PRIMIGRAVIDAS (MULTIGRAVIDAS, BOLD NUMBERS) [146]

Social class	Maternal age (y)	Number of births	Birth weight ≤ 2500 g	Per cent
Professional (salaried)	21-25	128	2	1.56
	26-30	177	13	2.08
	31-35	103	8	7.34
Manual workers (wages)	21-25	1452	118	2.68
	26-30	1013	66	7.77
	31-35	448	41	5.43

The table is mainly data on primigravidas; the lower line of percentages in bold type are equivalent data for multigravidas.

Here the sample size was constraining, $\chi^2 = 3.7453$, $p = 0.0530$ (1 degree of freedom). Moreover, the profile of results differed. The lower range of underweight infants has moved up the maternal age scale for wives of salaried professionals to include those 26-30 years old, and this age range among the wage earners is higher but not by much.

All of the other data treatments tried by Douglas came to the same result: the clearest distinction was for the youngest mothers from the highest social class, and they were the only group to achieve the low prevalence of low birth weight the study committee accepted as "satisfactory."

The number of women under 20 years in the highest social class was negligible and those cases were excluded by Douglas. He reported, however, 197 primigravid women ≤ 20 years from the lowest social class; 27 of these delivered infants weighing < 2500 grams, or 13.71 per cent, not quite twice the combined rate for ages 21-35. Similarly, there were 199 women from the lowest social class ≥ 36 years of age giving birth for the first time. Twenty-four delivered infants ≤ 2500 grams, or 12.1 per cent. The possible link to nutritional factors comes from the date of the survey, March 1946. Rationing was still in

place in Great Britain and postwar economic recovery was not yet under way; that did not occur in Western Europe until several years after the war.

The high rate of underweight infants for women less than 20 years old is a reminder that Finnerty and Bepko used girls *under 17 years of age* for the notorious thiazide study of 1966 [175]. The observations from Great Britain for 1946 were not clouded by patient noncompliance in medication or shifting of large groups of individuals in data analysis; they were simply the birth weight as measured for an age group [146]. More recently, Kaminetzky studied the effect of nutritional education on pregnant teenagers [275].

These girls were 13-17 years old, presumably comparable to those in the Finnerty trial (Finnerty did not give the lowest age of his study subjects). Kaminetzky followed 130 patients over the course of nutritional instruction and found an effective shift upward in both daily protein intake (Table 10-2) and overall diet assessment (Table 10-3). His basic conclusion was that gross undernutrition was very common in this age group.

Table 10-3 indicates an important social factor at work. The improvement in overall diet came from the third category, *fair*, without any change in the proportion of teenage diets rated as poor. Kaminetzky et al. reported all of their cases of preeclampsia came from either poor or borderline protein

Table 10-2
THE EFFECT OF NUTRITIONAL INSTRUCTION OF
PROTEIN INTAKE IN 130 TEEN AGE PREGNANCIES [275]

Daily protein intake	Participants taking at intake level	
	Before instruction	After instruction
30-60 g	61 (46.9%)	30 (23.1%)
61-100	65 (50.0%)	73 (56.2%)
101+	4 (3.1%)	27 (20.8%)

Percentages do not total to 100.0 due to rounding.

Table 10-3
OVERALL DIETARY ASSESSMENT IN TEEN AGE PREGNANCIES
AND THE EFFECT OF NUTRITIONAL INSTRUCTION [275]

Assessment category	Participant dietary assessment	
	Before instruction	After instruction
Excellent	22 (16.9%)	27 (20.8%)
Good	34 (26.1%)	49 (37.7%)
Fair	56 (43.1%)	35 (26.9%)
Poor	18 (13.8%)	18 (13.8%)

Percentages do not total to 100.0 due to rounding.

intake and, further, these young women had low caloric intake and vitamin B₆ levels.

An earlier, and often overlooked report from the mid-1930s, was summarized in 1944 by Bourne [50]. Adding food supplements to pregnancy care in two areas of Wales in 1934 and 1936 was followed by declines in *maternal mortality* from 7.20 and 6.65 per thousand to 4.77 and 3.75 per thousand respectively. Perinatal mortality was reported from only one region but there was much improvement, from 92 per thousand down to 59 per thousand, in just one year.

The point of reviewing such old data is this: the differences, reported by Douglas, which may be statistical discrepancies, require explanation if they are not artefacts of sampling. A biological explanation for these, and many other unusual findings, will not be easy. There are many areas of potential investigation. We will *start* with three: (1) the genetics of adverse pregnancy outcome, (2) evidence for metabolic compartmentalization, and (3) nutrient intake efficiency.

THE GENETICS OF TOXEMIA AND BIRTH SEQUENCES

Leon Chesley researched the question of a genetic factor in preeclamptic toxemia for nearly sixty years, ultimately obtaining a three generation spread with 96 per cent participation [99,111]. He has emphasized the great difficulty in making the diagnosis when the clinical presentation is mild [99], thereby reminding one and all the condition remains syndromic until the pathogenesis is fully developed. Most of the questionable cases have only transient hypertension. Cooper et al. recently summarized the accumulated information [111]. Pedigree data shows a greatly increased risk for the condition in blood relatives of afflicted women. Efforts to place this into the maternal HLA gene structure have failed, which is partial evidence against a controlling immunological factor in gestosis. The possibility of involvement by fetal genotype is weakened by a lack of concordance among monozygous twins, although supportive evidence comes from a study of donor oocyte pregnancies and some other factors such as when the woman herself is the product of an eclamptic pregnancy [111]. Cooper does not assess the principal potential confounding factors which have been under examination in this area for the past century. Chesley, for his part, had doubts over results which fit so closely the hypothesis of a single recessive gene (which the data seem to support) because: ". . . (the match) so close as to leave no margin for predisposing factors, some of which are beyond doubt" [99]. There are many cultural

factors of nutrition and life style which are transmitted through families, as environmental conditioning, so, for now, the genetic link is unproven.

A case, likely unique, which can be construed as evidence for a genetic factor, is a letter to the editor from Astin [13], describing a man whose first and second wives both died from severe preeclampsia. On the other hand, association between maternal thyroid function and endothelin, a product of vascular lining cells, is supportive of the metabolic-endocrine hypothesis [29], especially when combined with older work on the dynamics of uterine blood flow mediated through changes in glucose metabolism [28,453,454].

An observation, more physiologic than pathophysiologic, which demands explanation from within the biological imperative, is the tendency to repeat gestational age and birth weight in successive births to the same mother [20]. A sample of 454,358 single births in Norway between 1967 and 1973, when wartime conditions were inoperative, demonstrated a remarkable tendency for repeat performance in respect to all three categories: low birth weight, small for gestational age, and large for gestational age infants [20]. The relative risks for second pregnancies productive of small for gestational age infants was 3.4 and the comparable relative risk for repeat large for gestational age was 3.0. Both categories accounted for very large shares of their respective newborn population, 27.7 per cent and 21.2 per cent. Bakketeg et al. sought associations among complications during pregnancy and delivery. Some relative risks, for specific sequences, rise to remarkable levels. For example, a woman delivering two successive low birth weight infants (≤ 2500 g) has a relative risk for another one in the third confinement of 8.1. Of interest, biologically, is the graded response in intermediate sequences (Table 10-4) [20].

The rising risk with successive pregnancies can be viewed, genetically, as poor penetrance of the primary maternal genomic force, if there is one, unless there are multiple interactive alleles. Bakketeg et al. went one more step, simultaneous assessment of some combinations of outcome measures which reveal the strength of the underlying process (Table 10-5) [20]. They did not report the countertrends, i.e., low birth weight in the first or second pregnancy followed by preterm birth, which might have shown correlative tendencies. Nevertheless, the link between preterm delivery and low birth weight is well shown by the "yes-yes" line for both first and second pregnancies in both combinations, with respect to the risk subsequently. This information does not prove there is a genetic factor determining the fetal weight, but it does elevate the idea beyond speculation.

The study from Norway, at a time of reasonable prosperity and presumed good diet, has a graded and compelling logic missing from the immediate

Table 10-4
THE RISK FOR PRETERM DELIVERY OR LOW BIRTH
WEIGHT FOR SEQUENCES OF PREGNANCY OUTCOME [20]

Sequence of births		Subsequent birth (relative risk)	
		Preterm (<36 weeks)	Low birth weight (≤2500 grams)
First	Second		
A. Low birth weight			
No	--		1.0
Yes	--		4.1
No	No		0.6
Yes	No		1.7
No	Yes		2.8
Yes	Yes		8.1
			= 3.5
B. Preterm delivery			
No	--	1.0	
Yes	--	3.4	
No	No	0.6	
Yes	No	1.4	
No	Yes	2.1	
Yes	Yes	6.7	
			= 4.3

postwar data from Britain [146]. One would expect such a larger sample to provide smoother transitions between data groups but the results also support the equally appropriate idea that the 1946 British study showed fluctuation in part due to dietary instability.

Table 10-5
CONJOINT RISK FOR PRETERM DELIVERY OR LOW BIRTH WEIGHT
FOR SELECTED SEQUENCES OF PREGNANCY OUTCOME [20]

Sequence of births		Subsequent birth (relative risk)	
		Preterm (<36 weeks)	Low birth weight (≤2500 grams)
First	Second		
A. Low birth weight but not preterm			
No	--		1.0
Yes	--		5.5
No	No		0.8
Yes	Yes		19.3
B. Preterm delivery but not low birth weight			
No	--	1.0	
Yes	--	4.5	
No	No	0.9	
Yes	Yes	11.0	

MATERNAL METABOLIC COMPARTMENTALIZATION

The evidence for metabolic compartmentalization, as a feature of normal fetal growth and development, is better established than a genetic factor for gestosis, but has not been examined in pregnancy from other physiological perspectives. Rosso, an insightful researcher and writer in the field of pregnancy nutrition, once emphasized the binary nature of the situation under the term *maternal-fetal exchange*, which is always either directly or indirectly related to two fundamental characteristics. He was referring to (1) the total dependency of the fetus on maternal nutrient supply, and (2) the incapacity of the mother to supply nutrient throughout gestation on her own without replenishment from the outer environment [459].

Together, these factors are the first layer of the biological imperative. Left to her own devices, an American woman entering pregnancy with reasonable nutritional status, will take in a cumulative total of 84,000 kcal and 9,800 g of protein [459]. There is a metabolic cost to this intake and a metabolic cost to the transfer of the fetoplacental share. Rosso summarized experimental data from over twenty years ago which showed, in part from the work of Naismith [394], a time-related deposit of protein and fat in the maternal carcass. In the rat, this occurs only in the second week (of three) at a time when fetal needs are still low. There are changes in enzyme activity such as those related to synthesis of urea and hepatic catabolism. The sites of storage of protein and fat also differ with time. After two weeks the extra protein is in muscle; at the end of gestation, in liver (Table 10-6) [394,459]. The protein is structural, not as a depot [195].

Naismith proposed hormonal regulation of protein synthesis as the basis

Table 10-6
DISTRIBUTION OF ADDITIONAL NITROGEN RETAINED
BY PREGNANT RATS [ADAPTED FROM 394 AND 459]

Compartment	At day 14		At day 21		Per cent change, day 14-21
	mg	Per cent	mg	Per cent	
Total gain	748.6	100.0	1405.9	100.0	+187.8
Gestational products*	131.7	17.59	1185.6	84.33	+900.2
Maternal tissue					
Carcass	500.5	66.85	60.0	4.27	-99.1
Liver	85.6	11.43	125.1	8.90	+146.1

*Uterus, fetuses, placentas, amniotic fluid. Omitted from the table are other visceral tissues, which showed minimal change.

for this compartment shift in the third week of rat pregnancy and called attention to the correlation between progesterone level and protein synthesis but discounted its role in pregnancy since it is anabolic toward muscle tissue. The result, shown in Table 10-6, is closer to the catabolic effect on muscle of corticosteroids and this would be facilitated by reduced insulin sensitivity also seen in late pregnancy. These possibilities are supported in part by the differential effect by infant sex of dietary supplements, especially protein supplements; female infants are more sensitive to supplementation, with more improvement in a variety of outcome measures, including motor functions [549]. Comparable nitrogen retention has been demonstrated in humans [84,256].

Rosso [459] considered whether high protein "storage" would mean excessive water retention [256] but Grieve established water retention as a feature of carbohydrate intake [211-213], a result in line with the experimental work exculpating protein as the basis for water retention. Most protein synthesis is structural and the retention of water pursuant to this would be a part of structural integrity and function [181].

Total body water turnover differs in gestotic pregnancies [255]. Hutchinson et al. examined the point using deuterium oxide as an isotopic tracer. The normal water turnover is constant from <15 to 39 weeks, 7.9 per cent per day, changing only at the time of labor and delivery when the turnover varies widely (2-22% per diem). Women with gestosis have **low turnover**, 2-7 per cent per diem while the turnover for nongestotic hypertensives was normal to high, 8-14 per cent per diem.

Partition experiments demonstrate that if there is a true competition between the fetus and the mother, it is only for the excess nutrient taken in during gestation *per se* and not for structural protein present in the mother before conception [225]. Hammond's partition theory [225] has been confirmed in rats [181]. The timing of food intake has influence on blood glucose levels in gestational diabetes mellitus [469].

Partition experiments in rats, guinea pigs, pigs, and monkeys showed extreme low level protein or caloric intake to result mainly in high fetal mortality and a significant reduction in birth weight (upward to 25% in the guinea pig) with little effect on net maternal weight [181,577]. These and other similar work combine to indicate maternal metabolism is able to sequester some part of nutrient to maintain her own status, at the relative expense of the fetus, that is, to compartmentalize [459].

The role of specific pregnancy hormones in compartmentalization was extensively reviewed by Handwerger and Freemark [226]. The lack of somatotropic and metabolic activity of growth hormone (GH) is not due to low concentrations, which tend to exceed postnatal levels, but rather to a

deficiency of specific fetal GH receptors [183]. By contrast, placental lactogen has a particular role in stimulation of fetal hepatic ornithinedecarboxylase activity. This is a critical enzyme because it is the rate limiting step in the synthesis of polyamines, with critical roles in nucleoprotein and structural metabolism [254].

A metabolic compartment can be constructed conceptually for purposes of discussion by defining a function or biochemical need, as well as by specific substances or clusters of interactive substances. One such construct might be the antioxidant capacity of the body, the ability of tissues to neutralize or minimize free radical injuries to tissue [347].

Machlin and Bendich summarized the protective role of antioxidant nutrients with respect to free radical tissue damage [347]. A reactive molecule with one or more unpaired electrons is a free radical. These chemical species are relatively unstable and have the potential to harm cells and tissues. Oxygen free radicals form readily from many enzyme mediated and other biochemical reactions. Various enzymes and small molecules have antioxidant capability (Tables 10-7 & 10-8). Thus, the health of a tissue or cell requires a balance between free radical production and defensive attributes.

Table 10-7
INVENTORIES OF FREE RADICALS, THE CELLULAR SITES OF PRODUCTION, RELATED SUBSTANCES [347]

<i>Sites of free radical production</i>	<i>Free radicals</i>	<i>Related substances</i>
Mitochondria	hydroxyl-	hydrogen peroxide
Lysosomes	peroxy-	singlet oxygen
Peroxisomes	hypochlorite	
Nuclear membrane	superoxide	
Plasma membrane	alkoxy-	
Endoplasmic reticulum		
Cytosol		

Horizontal listing is not meant to imply exclusive site of manufacture.

Many foods contain antioxidant nutrients, which, in late 20th century America, are popular "vitamin" supplements (Table 10-8).

Many substances listed in Table 10-8 have reinforcing actions, viz, α -tocopherol protects conjugated double bonds of β -carotene from oxidation. Selenium, ascorbic acid, and β -carotene levels are lower in smokers (a smoking effect on fetal growth?) [101,105].

Relationships between nutrients and other environmental chemicals are now being explored in detail [10].

Table 10-8
PRINCIPAL ACTIONS OF MAJOR ANTIOXIDANT MICRONUTRIENTS [347]

Antioxidant micronutrients	Activities/properties
Ascorbic acid (vitamin C)	Chain-breaking antioxidant; direct superoxide reactant; direct singlet oxygen reactant; regenerates tocopherol from tocopheroxy radical
α -tocopherol (vitamin E)	Membrane bound, lipid soluble chain-breaking antioxidant reacts directly with superoxide, singlet oxygen
β -carotene	Most potent singlet oxygen quencher; antioxidant properties at low oxygen pressure, lipid soluble
Copper	Constituent of cytosolic superoxide dismutase and ceruloplasmin
Iron	Constituent of catalase
Manganese	Constituent of mitochondrial superoxide dismutase
Selenium	Constituent of glutathione peroxidase
Zinc	Constituent of cytosolic superoxide dismutase

NUTRIENT INTAKE EFFICIENCY

Typical schedules for meals are related partially to circadian physiological rhythms and partially to cultural conditioning and each factor influences the other. Protein retention depends on the timing of food intake [87,107,193,194,321,507,508,573].

Cohn et al. suggested in 1962 the *manner* of ingesting an otherwise adequate diet might have widespread influence on the health and nutritional status of the recipient. Experimental animals fed for limited time periods or force fed are considered equivalent to meal eating in humans; those given free access to nutrient are equated with nibbling. Two questions were raised with clinical relevance: (1) does mankind react to different feeding frequencies as do other animal species, and (2) do feeding habits contribute to some human metabolic diseases? The answer to both seems to be affirmative. For example, experimental diabetes is worsened by force feeding. Better control of juvenile diabetes is obtained by near "round the clock" feeding of glucose and provision of insulin [107].

Earlier work had established the same point experimentally in animals [87] and in humans [573].

Acute predelivery maternal intravenous infusions of amino acids, over a range of 0-75 minutes antepartum, significantly increases the fetal blood levels of most of the amino acids used, only three failing to show an increase: histidine, lysine, and threonine [451].

Adult male rats made protein deficient by dietary means will recover lost weight readily when fed repletion diets consisting of adequate calories, vitamins and minerals, and the ten essential amino acids as the principal source of protein. If the amino acids are split into aliquots with the other factors held constant, and these feedings are alternated, the animals will gain weight poorly. If the split diets are fed alternately along with protein depleted food for a large part of the 24-hour cycle, the animals continue to lose weight. If the two diets are put together and the mix is alternated with the depleted intake, the animals will regain weight rapidly [87]. Cannon considered the implication of these results to be clear: all essential amino acids must be available simultaneously for positive nitrogen balance in the form of protein synthesis. Timing is everything for short-term cell processes.

Wu and Wu studied a healthy male weighing 68.5 kg who had been on a free choice diet containing 78 grams protein per day in 2500 kcal. The clinical protocol was complex, calling for a fixed total diet of 78 grams of protein in 2500 kcal divided into allotments of 2, 3, or 4 meals for four days each. Follow-up trials three and four months later modified this with an eventual reduction in protein to 50 grams per diem. Nitrogen excretion was related to the meal schedule independent of the diurnal pattern and irrespective of the level of protein intake, for these time intervals [573].

When the rate of protein formation equals the rate of protein breakdown, the organism in question is in protein equilibrium. The concentration of amino acids in the metabolic pool fluctuates with feeding. The specific dynamic effect of protein is mainly, if not entirely, due to an increase in the rate of metabolism of amino acids, after the concentration rises with feeding. The oscillatory nature of this means alternating increased catabolism at the trough of the wave which may be compensated by increased anabolism at the crest, but the increased loss of amino acids by excretion and by urea formation at the crest is not equally compensated by a reverse reaction at the trough. Thus, the amount of nitrogen irreversibly removed from the pool depends on the frequency and amplitude of the waves of amino acid concentration which is the result of the feeding schedule [573].

A more sophisticated demonstration in young women of reproductive age was carried out by Leverton and Gram [321]. Briefly, one group had animal protein for breakfast in the form of milk and the other did not; the feedings

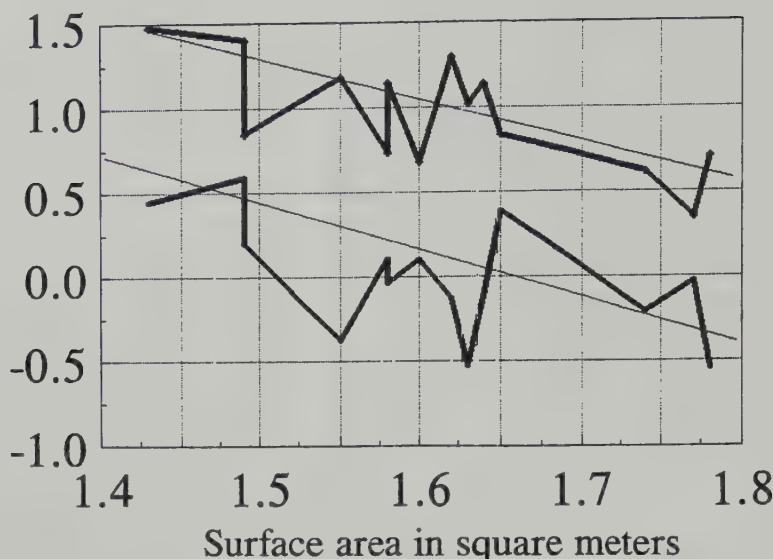
Nitrogen retention by body surface area

Figure 10-1. Nitrogen retention per day in grams versus total body surface area following ingestion of 62 grams of protein. The difference in the two scales is in the timing of protein intake. The upper curve resulted from adding 8 ounces of whole milk to breakfast and subtracting that aliquot of protein from the midday and evening meals.

were otherwise isocaloric with equivalent total amounts of animal protein. This pattern of distribution made a highly significant difference. The women fed animal protein at breakfast had consistently higher positive nitrogen balance inversely correlated with body surface area (Figure 10-1).

In discussion, Leverton and Gram noted the body has to have all essential amino acids present simultaneously and in adequate amounts for tissue synthesis [321]. This closely controlled study, in a small girls' school, confirmed Cannon's [87] conclusion: nitrogen retention and growth do not result when complementary paired proteins are fed alternately with measurable pauses between feedings. An informal version which biologically combined the work of Cannon and Leverton and Gram was reported by Williams [561].

A group of young pregnant women ended up with better nitrogen retention from high morning amino acid intakes because their breakfasts consisted of "leftovers" from the evening meal of the day before. Williams emphasized what should be an obvious point: there are no amino acid RDAs for pregnant women.

Total body ^{40}K and weight gain in teenage pregnant girls was carefully studied by King et al. in 1973 [284]. The average observed N retention was 2.4 g per day. On review of prior studies, King et al. noted that nitrogen

retention, measured in more than 50 pregnant women, was reported far in excess of theoretical accretion during pregnancy based on the types of calculations which misled Dieckmann [134]. Teenage pregnancy is further complicated by cultural mores regarding food among the age cohort [275]. King et al. concluded that until and unless further evidence is found, the National Research Council RDA for pregnancy protein should probably be based on a 30 per cent net nitrogen utilization (NNU) rather than 70 per cent, increasing the added protein allowance to about 30 gm/day, bringing the total to 85 gm/day, essentially Dieckman's paradoxical protein target. Per King et al: "As all women probably experience stress sometime during their pregnancy, an increase in protein intake is recommended."

This is another way of saying there are hidden costs of protein metabolism in pregnancy and one of them is the cost of an inefficient intake schedule. Waterlow, in a study of adaptation to low protein intake [554], emphasized from animal work that there is no *general* amino acid metabolic pool; rather, each amino acid is an independent metabolic compartment modified by the interactions with others which are linked biochemically, such as cysteine, cystine, and methionine, and their glycogenic effects [405]. Similar pathways indicate 58 per cent of protein and about 10 per cent of lipid is glycogenic [405]. These ratios have not been examined in pregnant women.

This emphasis on proteins should not draw away from the fact that effective nutritional intake is a mix of proteins, carbohydrates, lipids, and micronutrients. Snyder et al. found some evidence that carbohydrate content is a factor in the response to growth hormone in energy restricted humans [504] through a complex link with insulin growth factor I. The effects of growth hormone were examined in obese women with widely divergent nonprotein caloric intakes (Table 10-9). The divergent diets were either 80 per cent of nonprotein calories from carbohydrates or lipids at a total of 12 kcal per kilogram body weight.

Table 10-9
EFFECTS OF HIGH CARBOHYDRATE OR HIGH LIPID DIETS AND
GROWTH HORMONE (GH) ON URINARY NITROGEN EXCRETION
AND INSULIN LIKE GROWTH FACTOR I (IGF-I) (\pm S.E.M.) [504]

Diet intake at 80% nonprotein calories	Urinary nitrogen excretion (mmol/day) and insulin like growth factor I (nmol/L)			
	Base line	IGF-I	After GH	IGF-I
Carbohydrate excess	660 \pm 50	36.2 \pm 3.96	532 \pm 51	55.9 \pm 2.69
Lipid excess	794 \pm 81	31.0 \pm 2.90	743 \pm 56	41.7 \pm 3.94

Snyder et al. reported some statistical significance to urinary nitrogen excretion but recalculation of the t and p values fails to confirm their claim. These were very small samples (carbohydrate excess, n = 6 and lipid, n = 5), so this is not especially surprising, but what did tend toward significance were the tighter results from the assay for IGF-I [504]. The increase after GH for the carbohydrate primed subjects reached $t = 4.11$, $p = 0.076$ while that for lipid primed subjects was a nonsignificant $p = 0.1356$ (both as one-tailed t-tests). The statistical basis for their assertion is not available from the report but simultaneous tracking of the data trend supports a biological likelihood for their conclusion as to the process involved. The results are consistent with others discussed in this section, thus their inclusion, the statistical calculations notwithstanding.

Black and Goldberg and associates, in a series of important papers [40,41,201], examined the validity of dietary records against actual measurements of energy availability used in exercise physiology. A concept of minimal cutoff values for basic daily activities, applied to a review of 37 other published surveys, indicated conclusively that dietary recalls and so-called contemporaneous diaries have a strong bias for underreporting. They concluded the only fully quantitative method was a weighed diet record. These approaches have not yet been applied to human pregnancy.

Extended physiological stress which conflicts with diurnal phenomena, which is one way to characterize the accumulative nature of human gestation, is also seen in military personnel who underutilize rations when on maneuvers or in combat [220]. The concept of scheduled small meals more often across the 24-hour day, has been and is being evaluated for American military forces [359]. The concept of chronome, the time structure of the body, has been shown to have both a circadian and a longer, approximately seven-day periodicity or oscillation [220]. In apposition to studies (see above) which show better nitrogen retention when breakfast has good protein content, weight gain has been shown to follow much more readily when a single, full nutrient meal is at the dinner hour rather than for breakfast (one meal per day) [220]. No pregnant women were or are under study by military related research of this sort, but the principles would seem to be applicable to gestational nutritional physiology. Since the third trimester is the time of greatest weight accretion by the human fetus when the pressure of the expanding uterus most severely constrains meal size, a natural compromise has to be reached: frequent small meals are all that are practicable. What remains to be determined is their content, sequence, and schedule. The scenario has the built in prospect of intake becoming limited *below the needs of the biological imperative*, through the influence of social and cultural practices.

AFTERWORD

The author makes no claim that the vast subjects of nutrition, pregnancy metabolism, and their progeny, pregnancy nutrition, have been examined exhaustively. The positive words of my colleague, Professor Billy F. Andrews, as stated in his Foreword, are heartfelt, but we both know and understand, for a long time into the future, this will remain a work in progress. Hopefully, this book will be considered a constructive contribution to our future understanding.

As has been shown throughout, the state of nutrition during the most rapid stages of growth of the fetus and child has profound effects on mental development, physical growth, and health. The White House Conference on Food, Nutrition, and Health stressed the unequivocal relationship between nutrition and health. Their panel, "Pregnant and Nursing Women and Infants," issued the following statements:

Every woman has the right to high quality and high standard health care . . .
The right to adequate nutrition is an inseparable part of the basic right to health care and . . . [pregnant and lactating] women require and are entitled to sufficient amounts of nutritious foods. [603]

These are powerful words, at once hortatory and challenging, but direct. They require of modern medical science an effort equivalent to the melioristic tone of the paragraph, but one founded in the reality of mammalian biology, not in slogans. The complexity of the challenge suggests a modification of the famous criterion enunciated by the late Carl Edward Sagan (1934-1996),¹ ". . . extraordinary objectives require extraordinary endeavor . . ."

Many diverse prospective, anteroseptive, and retrospective clinical and field studies collectively document the causal relationship between malnutrition, especially during pregnancy, and a continuum of reproductive casualty, consisting of maternal and infant death, prenatal and paranatal complications, and neuropsychiatric, mental, and physical disorders of infancy and childhood. Furthermore, an analysis of the association between neurological dysfunction and low birth weight coupled with complications of pregnancy, shown to be accurate barometers of infant health and future development, confirmed the demonstrated relationship between malnutrition and developmental disabilities. The relationship between low birth weight and complications, which are physiologically and clinically linked to malnutrition, and a continuum of reproductive casualty have been examined

¹ "Extraordinary claims require extraordinary evidence."

by a thorough review of various longitudinal scientific studies. In addition, less accurate but somewhat reliable proxies for nutritional status, such as weight gain during pregnancy and prepregnancy weight, were shown to be highly correlated with birth weight and subsequent mental and physical development.

At the same, given the important advances in cell biology and human pathophysiology, it must be recognized that these exterior overt measurement indicia will remain forever indirect measures of what must occur within the smaller but definitively more important realm of protein chemistry.

Newer information and previously unconnected fields of investigation intrude from time to time, sometimes as points in evidence, sometimes as further challenges. As an example from the introduction to this book, the characterization of rare amino acid disorders [101,142,358,548] offers insights into developmental protein metabolism. Clinical events often pertain. Pregnancy in a woman with a kidney allograft ten years before conception (and off immunosuppressive medication for three years) was successful into the third trimester, reaching 35 weeks gestational age, but with a low birth weight male, at 2,175 grams [271].

One cannot dismiss the demographic factors [621] out of hand, and I do not do so. Rather, their position in the galaxy of information as well as their content have to be put back into the biological matrix. For example, in addition to failing to account for the personal and clinical features of the special peer group [275] and socioeconomic status of the public health clinics which provided the teenage pregnancies for thiazide testing [175], unemphasized was the stark fact there were only two white patients in the entire final cut of 3,083 individuals! The time frame, 1958 to 1962, was one of vastly different reproductive attainment, unfortunately, between whites and blacks. Dismissing two patients from the data will have no effect and it would be difficult enough to consider the effects of such factors as different tendencies to hypertensive disorders. It would be pure speculation at this late date, but one might wonder whether the potential uterine growth factor identified by Langlois [307] might have been relevant to the poor outcome of the study.

Similarly, one would rather like to have more appreciation and specific information on the role, if any, of Muirhead's medullipin system in human pregnancy [388,389], as it seems to induce an almost antigestotic state.

At the working phase of pregnancy: labor, delivery, and the initial neonatal adaptations, knowing in physicochemical and cellular terms the true meaning of the much abused word, *anoxia*, would carry benefit beyond clarification of the etymological fog the term has generated for a century or more.

If we limit our consideration to the documented historical results and ignore fundamental biological process and principles, then solutions to the individual, social, and public needs will continue to be underproductive. More specifically, a new review of The Womens-Infants-Children Program (WIC) should concentrate on the female children raised through that mechanism to determine their current health and *their knowledge of good pregnancy nutritional practice* with the view to modifying how they are to be fed optimally during their own subsequent individual pregnancies. There are some obvious gaps in what is known in addition to what has been applied in the clinical setting. The work of Rosso, Prentice and associates, Grieve, and many others point to the possibility of limits of assimilation of a mix of calories and proteins (said mix favoring the latter at the expense of the former, up to an undetermined degree) which now need to be put into a more basic knowledge of food adequacy and utilization, basic precepts of physiology which are not yet fully developed for human pregnancy.

For example, basal metabolic rates and nitrogen retention (protein synthesis) are most commonly reported as a result against body surface area in square meters. A close look at the insight gained by Rosso [460] on the lack of effect on birth weight of maternal weight gain beyond certain biological parameters offers further understanding of the limiting mechanism. Leverton and Gram found nitrogen retention, whether there was morning protein intake or not, to fall with increased surface area (in m^2). Pregnancy is one human growth condition in which significant weight gain occurs without an increase in height (progressive obesity in adults is the other). The formula for surface area is a complex exponential equation:

$$\text{Surface area } (\text{m}^2) = \text{Weight } (\text{kg})^{0.425} \times \text{Height } (\text{cm})^{0.725} \times 0.007184$$

Pregnancy change, with static height, converts the calculation to the effect of weight gain alone. Standard nomograms² show that a typical pregnancy weight gain of 10 kg will produce an increase in surface area of 0.1 m^2 with the further result of 0.2 gm less nitrogen retained per diem. From this perspective, excess maternal body mass achieved by very large weight gains will reach a point [460] where no benefit accrues to the fetus in terms of weight gain, and, taken to an extreme, may actually be harmful in the final weeks of pregnancy. It certainly is a feature with possible influence on nutrient partition mechanisms, and clearly a subject for further research.

This sense of the incompleteness of the mission does not give us license to ignore what is already known. This book, a review of various scientific studies which link poor nutrition to permanent neurological damage and

² Guyton, AC: Textbook of medical physiology, 7th ed., 1986, Saunders, Philadelphia, p. 848.

other handicapping conditions, coupled with a discussion of pertinent medical phenomena, has unequivocally demonstrated infant and childhood death and permanent neurological impairment are primary effects of malnutrition during pregnancy and early postnatal life. Clinical, veterinary, epidemiological, and dietary studies of recent decades have shown increasing awareness and comprehension of these problems [14,38,211,279,387,429, 487-490,525,621]; such studies must be continued and extended. Furthermore, these matters can and should be applied now in the clinical setting, both in public clinics [211] and in private practice [14]. The results will vary, depending on the degree to which the biological imperative *has been fulfilled prior to and during the earliest stages* of the individual pregnancies under consideration.

To that end, the discussions of physiological phenomena and the consequences of poor nutritional practice are intended to encourage adoption of comprehensive professional and lay education on scientific management during the most rapid neurological development of the human fetus and child. It is the wish of the author that this review will enlighten public and private health care professionals and generate a public awareness and discussion regarding the highly significant extent to which inadequate nutrition leads to permanent mental and physical impairment and death in infants and children.

Nationwide cooperative efforts to provide proper nutrition for those *impoverished for any component of knowledge and resource* during critical stages of neurological development would seem to be the least obligation of a society which has the means to sustain itself adequately in the larger economic sense. Proper professional awareness, and fully informed patients, acting together, will promote the abandonment of both iatrogenic and patient originated malnutrition during pregnancy. Let us renew ourselves to the task.

REFERENCES

1. Abramowicz, M. & Kass, E.H.: Pathogenesis and prognosis of prematurity. *New Engl J Med*, 275:878-885, 1966.
2. _____: 275:938-943, 1966.
3. _____: 275:1053-1959, 1966.
4. Abrams, B.: Preventing low birth weight: does WIC work? A review of evaluations of the special supplemental food program for women, infants, and children. *Ann NY Acad Sci*, 678:306-316, 1993.
5. Abrams, B. & Parker, J.D.: Maternal weight gain in women with good pregnancy outcome. *Obstet Gynecol* 76:1-7, 1990.
6. Acker, D.B. et al.: Risk factors for shoulder dystocia. *Obstet Gynecol* 66:762-768, 1985.
7. Acosta-Sison, H.: Relation between the state of nutrition of the mother and the birth weight of the fetus: A preliminary study. *J Philippine Islands Med Assoc* 9:174-176, 1929.
8. Aladjem, S., et al.: Effect of maternal glucose load on fetal activity. *Am J Obstet Gynec*, 134:276-280, 1979.
9. Alberman, E. et al.: Disabilities in survivors of low birthweight. *Arch Dis Childh*, 60:913-919, 1985.
10. Anderson, K.E. et al.: Nutrient regulation of chemical metabolism in humans. *Fed Proc*, 44:130-133, 1985.
11. Antonov, A.N.: Children born during the siege of Leningrad in 1942. *J Pediatr*, 30:250-259, 1947.
12. Applebaum, R.M.: The obstetrician's approach to the breasts and breast-feeding. *J Reprod Med*, 14:98-116, 1975.
13. Astin, M. et al.: Pre-eclampsia: a fatal father factor. *Lancet*, ii:533, 1981 (letter).
14. Atkinson, S.M.: Salt, water, and rest as a preventative for toxemia of pregnancy. *J Reprod Med*, 9:223-228, 1972.
15. Babson, S.G., et al.: Growth and development of twins of dissimilar size at birth. *Pediatrics*, 33:327-333, 1964.
16. Bacola, E. et al.: Perinatal and environmental factors in late neurogenic sequelae. I. Infants having birth weights under 1,500 grams. *Am J Dis Child*, 112:359-368, 1966.

17. Bacola, E. et al.: Perinatal and environmental factors in late neurogenic sequelae. II. Infants having birth weights from 1,500 to 2,500 grams. *Am J Dis Child.*, 112:369-374, 1966.
18. Bainbridge, R. & Tsang, R.: Optimal nutrition in low birth weight infants. In: Lifshitz, F: *Childhood nutrition*, 1995, Boca Raton, FL: CRC Press, pp. 33-42.
19. Baird, D.: Contribution of obstetrical factors to serious physical and mental handicap in children. *J Obstet Gynaecol Br Empire*, 66:743-747, 1959.
20. Bakketeg, L.S. et al.: The tendency to repeat gestational age and birth weight in successive births. *Am J Obstet Gynecol*, 135:1086-1102, 1979.
21. Baldwin, V.J.: Pathology of multiple pregnancy, 1994, New York: Springer Verlag, 409 pp. ISBN 0-387-94011-1.
22. Balfour, M.I.: Supplementary feeding in pregnancy. *Lancet* 1:208-211, 1944.
23. Balfour, M.I.: Nutrition of expectant and nursing mothers: Interim report of the People's League for Health. *Lancet* 2:10-12, 1942.
24. Ballantyne, J.W.: *Manual on antenatal pathology and hygiene: The foetus*, Edinburgh, W Green & Sons, 1902; also, _____: *Manual on antenatal pathology and hygiene: The embryo*, Edinburgh, W Green & Sons, 1904.
25. Banker, B.Q. & Larroche, J-C.: Periventricular leukomalacia of infancy. A form of neonatal anoxic encephalopathy. *Arch Neurol*, 7:386-410, 1962.
26. Barden, T.P.: Premature labor. *Continuing Educ*, June 1974, pp 19-22.
27. Barrera-Moncada, G.: Estudios sobre alteraciones del crecimiento y del desarrollo psicológico del síndrome pluricarencial (kwashiorkor), 1963, Edtora Grafos, Caracas.
28. Barton, M.D. et al.: Response of ovine uterine blood flow to epinephrine and norepinephrine. *Proc Soc Exp Biol Med*, 145:996-1003, 1974.
29. Basbug, M. et al.: Correlation between maternal thyroid function tests and endothelin in pre-eclampsia-eclampsia. *Obstet Gynecol*, 94:551-558, 1999.
30. Bassett, J.M. & Madill D.: The influence of maternal nutrition on plasma hormone and metabolite concentrations of foetal lambs. *J Endocrinol*, 61:465-477, 1974.
31. Battaglia, F.C.: Metabolic aspects of fetal and neonatal growth. *Early Human Develop*, 29:99-106, 1992.
32. Battaglia, F.C. & Lubchenco, L.O.: A practical classification of newborn infants by weight and gestational age. *J Pediat*, 71:159-163, 1967.
33. Bennett, M.R.: Development of neuromuscular synapses. *Physiol Rev*, 63:915-1048, 1983.
34. Benton, A.L.: Behavioral indices of brain injury in school children. *Child Dev*, 33:199-208, 1962.
35. Berger, G. et al.: Regionalized perinatal care: An estimate of its potential on racial differences in perinatal mortality in North Carolina. *NC Med J*, 36:476-479, 1975.
36. Bernstein, I.M. et al.: Maternal insulin sensitivity and cord blood peptides: Relationships to neonatal size at birth. *Obstet Gynecol*, 90:780-783, 1997.
37. Binienda, Z. et al.: Effect of food withdrawal on arterial blood glucose and plasma 13,14-dihydro-15-ketoprostaglandin F concentrations and nocturnal

- myometrial electromyographic activity in the pregnant rhesus monkey in the last third of gestation. *Am J Obstet Gynecol*, 160:746-750, 1989.
38. Birch, H.: Functional effects of fetal malnutrition. *Hosp Practice*, March 1971, pp 134-148.
39. Birch, H. & Gussow, J: *Disadvantaged children: Health, nutrition and school failure*. New York: Grune & Stratton, 1970.
40. Black, A.E. et al.: Critical evaluation of energy intake data using fundamental principles of energy physiology. 2. Evaluating the results of published surveys. *Eur J Clin Nutr*, 45:583-599, 1991.
41. Black, A.E. et al.: Measurements of total energy expenditure provide insights into the validity of dietary measurements of energy intake. *J Am Dietet Assoc*, 93:572-579, 1993.
42. Bland, R.: Cord-blood total protein level as a screening aid for the idiopathic respiratory distress syndrome. *New Engl J Med*, 287:9-13, 1972.
43. Bland, R.D. et al.: Early albumin infusion of infants at risk for respiratory distress. *Arch Dis Childh*, 48:800-805, 1973.
44. Blekta, M. et al.: Volume of whole blood and absolute amount of serum proteins in the early stage of late toxemia of pregnancy. *Am J Obstet Gynecol*, 106:10-13, 1970.
45. Blickstein, I. et al.: Growth discordancy in appropriate for gestational age, term twins. *Obstet Gynecol*, 72:582-584, 1988.
46. Blumenthal, I: Diet and diuretics in pregnancy and subsequent growth of offspring. *Br Med J*, 2:733, 1976.
47. Boehm, F.H.: Presidential address: Can society afford perinatal health care? *South Med J*, 76:155-157, 1983.
48. Booss, B. & Bleeker, D.D.: Topology and analysis; the Atiyah-Singer Index formula and gauge-theoretic physics. New York: Springer-Verlag, 1985, p. 1.
49. Botto, L.D. et al.: Periconceptional multivitamin use and the occurrence of conotruncal heart defects: results from a population-based, case-control study. *Pediatrics*, 98:911-917, 1996.
50. Bourne, A.W.: Foetal development. *Proc Nutri Soc*, 2:1-6, 1944.
51. Bower, D.: The influence of dietary salt intake on pre-eclampsia. *J Obstet Gynaecol Br Commonw*, 71:123-125, 1964.
52. Brenner, W.E. et al.: A standard for fetal growth for the U.S.A. *Am J Obstet Gynecol*, 126:555-564, 1976.
53. Brewer, G.S.: *What every pregnant woman should know: The truth about diets and drugs in pregnancy*. New York: Random House, 1977, p 19.
54. Brewer, T.H.: Limitations of diuretic therapy in the management of severe toxemia: The significance of hypoalbuminemia. *Am J Obstet Gynecol*, 83:1352-1359, 1962.
55. _____: Role of malnutrition, hepatic dysfunction, and gastrointestinal bacteria in the pathogenesis of acute toxemia of pregnancy. *Am J Obstet Gynecol*, 84:1253-1256, 1962.
56. _____: *Metabolic toxemia of late pregnancy: A disease of malnutrition*. Springfield, IL: Charles C Thomas, 1966.

57. _____: Metabolic toxemia of late pregnancy: A disease entity. *Gynaecologia*, 167:1-8, 1969.
58. _____: Metabolic toxemia: The mysterious affliction. *J Appl Nutr*, 24:56-63, 1972.
59. _____: Pancreatitis in pregnancy (letter). *J Reprod Med*, 12:204, 1974.
60. _____: Iatrogenic starvation in human pregnancy. *Medikon*, 4:14-15, 1974.
61. _____: Metabolic toxemia of late pregnancy in a county prenatal nutrition education project: A preliminary report. *J Reprod Med*, 13:175-176, 1974.
62. Bridge, E.M.: *Epilepsy and convulsive disorders in children*. New York: McGraw-Hill, 1949.
63. Briend, A.: Do maternal energy reserves limit fetal growth? *Lancet* 1:38-40, 1985.
64. Briscoe, C.C.: Delivery of the premature infant. *Clin Obstet Gynecol*, 7:695-706, 1964.
65. Bronzino, J.D. et al.: Effect of protein malnutrition on hippocampal kindling: electrographic and behavioral measures. *Brain Research*, 384:348-354, 1986.
66. Bronzino, J.D. et al.: Effects of prenatal protein malnutrition on perforant path kindling in the rat. *Brain Research*, 515:45-50, 1990.
67. Bronzino, J.D. et al.: Effects of prenatal protein malnutrition on kindling-induced alterations in dentate granule cell excitability. I. Synaptic transmission measures. *Exper Neurol*, 112:206-215, 1991.
68. Bronzino, J.D. et al.: Effects of prenatal protein malnutrition on kindling-induced alterations in dentate granule cell excitability. II. Paired-pulse measures. *Exper Neurol*, 112:216-223, 1991.
69. Brown, M.C.: Pregnancy in a patient on home parenteral nutrition. *Br Med J*, 286:1060-1061, 1983.
70. Brzosko, W. et al.: Analiza immunohistochemiczna mas wloknikowatych w lozysku ludzkim. *Ginekol Polska*, 36:121-130, 1965.
71. Brzosko, W. et al.: Immunohistochemical analysis of the fibrinoid masses in human placenta. *Pol Med J*, 5:114-123, 1965.
72. Buchanan, T.A., et al.: Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. *Am J Obstet Gynec*, 162:1008-1014, 1990.
73. Buchanan, T.A.: Glucose metabolism during pregnancy: Normal physiology and implications for diabetes mellitus. *Israel J Med Sci*, 27:432-441, 1991.
74. Buescher, P.A. et al.: Source of prenatal care and infant birth weight: the case of a North Carolina county. *Am J Obstet Gynec*, 156:201-210, 1987.
75. Burger, G. et al. (Eds): *Malnutrition and starvation in western Netherlands*: September 1944-July 1945. The Hague, General State Printing Office, 1948.
76. Burke, B.S. et al.: Nutrition studies during pregnancy. I. Problem, methods of study and group studied. *Am J Obstet Gynecol*, 46:38-52, 1943.

77. Burke, B.S. et al.: Nutrition studies during pregnancy. IV. Relation of protein content of mother's diet during pregnancy to birth length, birth weight, and condition of infant at birth. *J Pediatr*, 23:506-515, 1943.
78. Burke, B.S. et al.: The influence of nutrition during pregnancy upon the condition of the infant at birth. *J Nutri*, 26:569-583, 1943.
79. Burnol, A-F., et al.: Insulin resistance of glucose metabolism in isolated brown adipocytes of lactating rats. Evidence for a post-receptor defect in insulin action. *Biochem J* 265:511-517, 1990.
80. Burton, G.J. et al.: Maternal arterial connections to the placental intervillous space during the first trimester of human pregnancy: The Boyd Collection revisited. *Am J Obstet Gynecol*, 181:718-724, 1999.
81. Butler, N.R. & Alberman, E.D.: *Perinatal problems* (National Birthday Trust Fund Study). Edinburgh: E & S Livingstone, Ltd, 1969, p 126.
82. Butte, N.F. et al.: Protein metabolism in insulin-treated gestational diabetes. *Diabetes Care* 22:806-811, 1999.
83. Cabak, V. & Najdanovic, R.: Effect of undernutrition in early life on physical and mental development. *Arch Dis Childh*, 40:532-534, 1965.
84. Calloway, D.H.: Nitrogen balance during pregnancy. In: Winick, M.: *Nutrition and fetal development*, New York: Wiley, 1974, pp. 79-94.
85. Cameron, C.S. & Graham, S.: Antenatal diet and its influence on stillbirths and prematurity. *Glasgow Med J*, 24:1-7, 1944.
86. Cameron, J. et al.: Infant vocalizations and their relationship to mature intelligence. *Science*, 157:331-332, 1967.
87. Cannon, P.R. et al.: The influence of time of ingestion of essential amino acids upon utilization in tissue-synthesis. *Fed Proc*, 6:390, 1947 (abstract).
88. Carter, B.S. et al.: A review of placental transport and fetal and placental metabolism of amino acids. *J Nutr Biochem*, 2:4-13, 1991.
89. Casalino, M.: Intrauterine growth retardation: A neonatologist's approach. *J Reprod Med*, 14:248-250, 1975.
90. Cetin, I. et al.: Maternal concentrations and fetal-maternal concentration differences of plasma amino acids in normal and intrauterine growth-restricted pregnancies. *Am J Obstet Gynecol*, 174:1575-1583, 1996.
91. Champakan, S.S. et al.: Kwashiorkor and mental development. *Am J Clin Nutr*, 21:844-855, 1968.
92. Chase H.: Trends in low birth weight ratios. *US Department of Health, Education, and Welfare*, 1973.
93. Chase, H.P. et al.: Undernutrition and cerebellar development. *Nature*, 221:554-555, 1969.
94. Chase, H.P. & Martin, H.P.: Undernutrition and child development. *New Eng J Med*, 282:933-976, 1970.
95. Chen, J-C., et al.: Prenatal protein malnutrition in rats enhances serotonin release from hippocampus. *J Nutr*, 122:2138-2143, 1992.
96. Chesley, L.C.: Sodium, diuretic drugs, and pre-eclampsia. *Patol Clin Obstet Ginecol*, 2:1-6, 1974.
97. Chesley, L.C.: The renin-angiotensin system in pregnancy. *J Reprod Med*,

- 15:173-180, 1975.
98. Chesley, L.C.: *Hypertensive disorders in pregnancy*. New York: Appleton-Century Crofts, 1978, p 6, (628 pp).
 99. Chesley, L.C.: The genetics of pre-eclampsia. *Hyperten Preg*, 12:vii-x, 1993.
 100. Chow, C.K. et al.: Low levels of vitamin C and carotenes in plasma of cigarette smokers. *J Am Coll Nutr*, 5:305-312, 1986.
 101. Chow, C.W. et al.: Neuropathology in glutaric aciduria type 1. *Acta Neuropath*, 76:590-594, 1988.
 102. Chowdhury, N.N.R.: Role of protein deficiency in toxemias of pregnancy. *J Ind Med Assoc*, 62:233-235, 1974.
 103. Churchill, J.: The relationship between intelligence and birth weight in twins. *Neurology*, 15:341-347, 1965.
 104. Churchill, J. et al.: Birth weight and intelligence. *Obstet Gynecol*, 28:425-429, 1966.
 105. Cnattingius, S. et al.: The influence of gestational age and smoking habits on the risk of subsequent preterm deliveries. *N Eng J Med*, 341:943-948, 1999.
 106. Cockburn, F. et al.: The influence of pre-eclampsia and diabetes mellitus on plasma free amino acids in maternal, umbilical vein and infant blood. *J Obstet Gynaecol Br Commonw*, 78:215-231, 1971.
 107. Cohn, C. et al.: Nutritional effects of feeding frequency. *Am J Clin Nutr*, 11:356-361, 1962.
 108. Cokington, L. et al.: Changes in body composition of malnourished infants during repletion. *Ann NY Acad Sci*, 110:849-860, 1963.
 109. Considine, R.V. et al.: The hypothalamic leptin receptor in humans: identification of incidental sequence polymorphisms and absence of the db/db mouse and fa/fa rat mutations. *Diabetes*, 45:992-994, 1996.
 110. Conway, D.L. & Langer, O.: Effects of new criteria for type 2 diabetes on the rate of postpartum glucose intolerance in women with gestational diabetes. *Am J Obstet Gynecol*, 181:610-614, 1999.
 111. Cooper, D.W. et al.: Genetics of pre-eclampsia. *Hyperten Preg*, 12:1-23, 1993.
 112. Corner, G.W., & Csapo, A.: Action of the ovarian hormones on uterine muscle. *Brit Med J* 1:687-693, 1953.
 113. Corruccini, C.G.: Nutritional management of obese pregnant women. *Bull Pan Am Health Organ*, 13:201-205, 1979 (condensed report).
 114. Coursin, D.B.: Maternal nutrition and the offspring's development. *Nutr Today*, March/April 1973, pp 12-18.
 115. Cravioto, J. & Robles, B: Evolution of adaptive and motor behavior during rehabilitation from kwashiorkor. *Am J Ortho-psychiatry*, 35:449-464, 1966.
 116. Crocker, J.F.S.: Renal anomalies in whole human embryonic culture. *Clin Res*, 20:915, 1972.
 117. Czeizel, A.E. & Dudas, I.: Prevention of neural tube defects by periconceptional vitamin supplementation. *New Eng J Med*, 327:1832-1835, 1992.
 118. Darby, W.J. et al.: The Vanderbilt cooperative study of maternal and infant nutrition. I. Background. II. Methods. III. Description of the sample and data. *J Nutr*, 51:539-563, 1953.

119. Darby, W.J. et al.: The Vanderbilt cooperative study of maternal and infant nutrition. IV. Dietary, laboratory and physical findings in 2,129 delivered pregnancies. *J Nutr*, 51:565-597, 1953.
120. Davidson, M.B.: Insulin resistance of late pregnancy does not include the liver. *Metabolism*, 33:532-537, 1984.
121. Davies, D.P. & Evans, T.J.: Nutrition and early growth of preterm infants. *Early Human Develop*, 2:383-392, 1979.
122. Davies, D.P. & Evans, T.J.: Reply (to Gaull, op cite) *Early Human Develop*, 2:376-378, 1979.
123. Davies, P.A., Feeding the newborn baby. In: Kodicek, E.: Nutrition of the foetus and the newly born. *J Nutr*, 28:66-72, 1969.
124. Dean, R.F.: Spec Rep Ser, Medical Research Council, No. 275, 1951, HMSO, London (Cited by Widdowson [560]).
125. Deb, A.K. & Cama, H.R.: Studies on human lactation. Dietary nitrogen utilization during lactation, and distribution of nitrogen in mother's milk. *Br J Nutr*, 16:65-73, 1962.
126. Decaisne, E.: Des modifications que subit le lait de femme par suite d'une alimentation insuffisante. Observations recueillies pendant le siège de Paris. *Gazette Medicale Paris*, 26: 317, 1871.
127. DeFronzo, R.A., et al.: The glucose clamp technique. A method for the quantifying of insulin secretion and resistance. *Am J Physiol*, 237:E214-E223, 1979.
128. Deitch, E.A. et al.: Management of burns in pregnant women. *Surg Gynecol Obstet*, 161:1-4, 1985.
129. Delgado, H.L., et al.: Nutrition, lactation, and birth interval components in rural Guatemala. *Am J Clin Nutr*, 35:1468-1476, 1982.
130. De Souza, S.W. et al.: Studies on the effect of maternal pre-eclamptic toxemia on placental weight and on head size and birth weight of the newborn. *Br J Obstet Gynecol*, 83:292-298, 1976.
131. Devadas, R.P.: Animal and human feeding studies on the biological availability of protein in supplements. *Adv Exp Biol Med*, 105:67-77, 1978.
132. Diáz-Cintra, S. et al.: Effects of protein deprivation on pyramidal cells of the visual cortex in rats of three age groups. *J Comp Neurol*, 292:117-126, 1990.
133. Diáz-Cintra, S. et al.: Effects of prenatal protein deprivation on postnatal development of granule cells in the fascia dentata. *J Comp Neurol* 310:356-364, 1991.
134. Dieckmann, W.J. et al.: Diet regulation and controlled weight in pregnancy. *Am J Obstet Gynecol*, 50:701-712, 1945.
135. _____ et al.: Observations on protein intake and the health of the mother and baby. I. Clinical and laboratory findings. *J Am Diet Assoc*, 27:1046-1052, 1951.
136. _____ et al.: Observations on protein intake and the health of the mother and baby. II. Food intake. *J Am Diet Assoc*, 27:1053-1058, 1951.
137. DiFederico, E. et al.: Pre-eclampsia is associated with widespread apoptosis of placental cytotrophoblasts within the uterine wall. *Am J Pathol*, 155:293-301,

- 1999.
138. Dobbing, J.: Undernutrition and the developing brain: the use of animal models to elucidate the human problem. *Psychiat Neurol Neurochir*, 74:432-442, 1971.
 139. Dobbing, J.: The later growth of the brain and its vulnerability. *Pediatr* 53:2-6, 1974.
 140. Dobbing, J. & Sands, J.: Growth and development of the brain and spinal cord of the guinea pig. *Brain Res*, 17:115-123, 1970.
 141. Dobbing, J. & Sands, J.: Vulnerability of developing brain. IX. The effect of nutritional growth retardation on the timing of the brain growth-spurt. *Biol Neonat*, 19:363-378, 1971.
 142. Dobyns, W.B.: Agenesis of the corpus callosum and gyral malformations are frequent manifestations of nonketotic hyperglycinemia. *Neurology*, 39:817-820, 1989.
 143. Dodge, E. & Frost, T.: Relation between blood plasma proteins and toxemias of pregnancy. *JAMA*, 111:1898-1902, 1938.
 144. Donnet, M.L. & Stanfield, J.P.: A survey of infant nutrition, growth and development in Glasgow. *Nutr Metabol*, 21(Supp 1): 220-222, 1977 [Scotland]
 145. Douglas, B.H.: *Experimental approaches to toxemia of pregnancy*. Springfield, IL: Charles C Thomas, 1971, pp. 14-25.
 146. Douglas, J.W.B.: Some factors associated with prematurity. The results of a national survey. *J Obstet Gynaecol Br Emp*, 57:143-170, 1950.
 147. Drillien, C.M.: The social and economic factors affecting the incidence of premature birth. Part I. Premature births without complications of pregnancy. *J Obstet Gynaecol Br Emp*, 64:161-184, 1957.
 148. _____: Growth and development in a group of children of very low birth weight. *Arch Dis Childh*, 33:10-18, 1958.
 149. _____: A longitudinal study of the growth and development of prematurely and maturely born children. II. Physical development. *Arch Dis Childh*, 33:423-431, 1958.
 150. _____: Physical and mental handicap in the prematurely born. *J Obstet Gynaecol Br Emp*, 66:721-728, 1959.
 151. _____: The incidence of mental and physical handicaps in school-age children of very low birth weight. *Pediatrics*, 27:452-464, 1961.
 152. _____: School disposal and performance for children of different birthweight born 1953-1960. *Arch Dis Childh*, 44:562-570, 1969.
 153. Eastman, N.J.: Obstetrical background of 753 cases of cerebral palsy. *Obstet Gynecol Surv*, 17:459-497, 1962.
 154. Eastman, N.J. & Hellman, L.M.: *Williams obstetrics*, 12th ed. New York: Appleton-Century-Crofts, 1961.
 155. Ebbs, J.H. et al.: The influence of prenatal diet on the mother and child. *J Nutr*, 22:515-526, 1941.
 156. Ebbs, J.H. et al.: Nutrition in pregnancy. *Canad Med Assoc J*, 46:1-6, 1942.
 157. Ebbs, J.H. et al.: The influence of improved prenatal nutrition upon the infant. *Canad Med Assoc J*, 46:6-8, 1942.

158. Edozien, J.C., et al.: Human protein deficiency: results of a Nigerian village study. *J Nutr*, 106:312-328, 1976.
159. Ehrlich, E.N.: Sodium metabolism in pregnancy: Current views. *Contemp Obstet Gynecol*, 4:17-19, 1974.
160. Eichenwald, H.F. & Fry, P.C.: Nutrition and learning: Inadequate nutrition in infancy may result in permanent impairment of mental function. *Science*, 163:644-648, 1969.
161. Emmanouilides, G.C. & Moss, A.J.: Respiratory distress in the newborn: effect of cord clamping before and after onset of respiration. *Biol Neonat*, 18:363-368, 1971.
162. Enders, R.H. et al.: Placental amino acid uptake. III. Transport systems for neutral amino acids. *Am J Physiol*, 230:706-710, 1976.
163. Engleston, G. et al.: A follow-up study of dysmature infants. *Arch Dis Childh*, 38:62-65, 1963.
164. Esterly, N.B.: The obstetrician and breast feeding: some views of women physicians. *J Reprod Med*, 14:89-97, 1975.
165. Eyler, F.D. & Behnke, M.: Early development of infants exposed to drugs prenatally. *Clin Perinatol*, 26:107-150, 1999.
166. Farmer, A.P.: Malnutrition as an ecologic problem. *E Afr Med J*, 37:399-404, 1960.
167. Fee, B.A. & Weil, W.B. Jr.: Body composition of infants of diabetic mothers by direct analysis. *Ann NY Acad Scien*, 110:869-897, 1963.
168. Feingold, B.: *Why your child is hyperactive*. New York, Random House, 1975.
169. Felig, P. et al.: Amino acid metabolism during prolonged starvation. *J Clin Invest*, 48:584-594, 1969.
170. Felig, P. et al.: Plasma amino acid levels and insulin secretion in obesity. *N Engl J Med*, 281:811-816, 1969.
171. Felig, P. & Lynch, V.: Starvation in human pregnancy: hypoglycemia, hypoinsulinemia, and hyperketonemia. *Science*, 170:990-992, 1970.
172. Felig, P. et al.: Amino acid metabolism during starvation in human pregnancy. *J Clin Invest*, 51:1195-1202, 1972.
173. Ferguson, J.H.: Maternal death in the rural South: A study of forty-seven consecutive cases. *JAMA*, 146:1388-1393, 1951.
174. Fernstrom, J.D. & Wurtman, R.J.: Nutrition and the brain. *Sci Amer*, 230 (February):84-91, 1974.
175. Finnerty, F.A., Jr. & Bepko, F.J., Jr.: Lowering the perinatal mortality and the prematurity rate. *JAMA*, 195:429-432, 1966.
176. Flowers, C.E., Jr.: Editorial: Nutrition in pregnancy. *J Reprod Med*, 7:200-204, 1971.
177. Flowers, C.E., Jr. et al.: Chlorothiazide as a prophylaxis against toxemia of pregnancy: A double blind study. *Am J Obstet Gynecol*, 84:919-929, 1962.
178. Fomon, S.J. & Ziegler, E.E.: Protein intake of premature infants: interpretation of data. *J Pediatrics*, 90:504-506, 1977.
179. Fondu, P.: A reassessment of intravascular volume measurements in protein-

- calorie malnutrition. *Eur J Clin Invest*, 7:161-165, 1977.
180. Fort, AT: Adequate prenatal nutrition. *Obstet Gynecol*, 37:286-288, 1971.
 181. Frazer, J.F.D., & Higgett, A.St.G.: The partition of nutrients between mother and conceptuses in the pregnant rat. *J Physiol*, 207:783-788, 1970.
 182. Freemark, M. et al.: Placental lactogen (PL) and growth hormone (GH) binding sites in sheep liver: striking differences in ontogeny and function. *Am J Physiol*, 251:E328-E333, 1986.
 183. Freemark, M. et al.: Nutritional regulation of the placental lactogen receptor in fetal liver: implications for fetal metabolism and growth. *Endocrinol*, 125:1504-1512, 1989.
 184. Freinkel, N. et al.: Facilitated anabolism in late pregnancy: Some novel maternal compensations for accelerated starvation. In: Malaisse, W.J. & Pirart, J. (Eds.): *Proceedings of the VIII Congress of the International Diabetes Federation*, Amsterdam, Excerpta Medica, 1974.
 185. Freud, S.: *Die Infantile Cerebrallähmung*. Vienna: Alfred Holder, 1897.
 186. Friedman, E.A.: *Obstetrical decision making*. Trenton, NJ: B.C. Decker, Inc., 1982, 222 p.
 187. Friis-Hansen, B.: Changes in body water compartments during growth. *Acta Paediat* 46:Suppl. 110:207-208(Summary), 1957.
 188. Gaito, J.: The kindling effect. *Physiol Psychol*, 2:45-50, 1974.
 189. Galler, J.R. et al.: A follow-up study of the influence of early malnutrition on subsequent development: 4. Intellectual performance during adolescence. *Nutrition Behav*, 3:211-221, 1986.
 190. Gaull, G.E. et al.: Milk protein quantity and quality in low-birth-weight infants. III. Effects of sulfur-containing amino acids in plasma and urine. *J Pediatrics*, 90:348-355, 1977.
 191. Gaull, G.E. et al.: Protein intake of premature infants: a reply. *J Pediatrics*, 90:507-510, 1977.
 192. Gaull, G.E. et al.: Nutrition and early growth of preterm infants. *Early Human Develop*, 3:373-378, 1979.
 193. Geiger, E.: Experiments with delayed supplementation of incomplete amino acid mixtures. *J Nutr*, 34:97-111, 1947.
 194. Geiger, E.: The role of the time factor in feeding supplementary proteins. *J Nutr*, 36:813-819, 1948.
 195. Ghadimi, H: The silent emergency: iatrogenically enhanced substrate deficiency in premature infants. *Am J Clin Nutr*, 30:1147-1152, 1977.
 196. Ghosh, A.K.: Influence of low standard of nutrition on the growth and development of the liveborn fetus. *J Ind Med Assoc*, 62:235-239, 1974.
 197. Girard, J.R. et al.: Fetal metabolic response to maternal fasting in the rat. *Am J Physiol*, 232:E456-E463, 1977.
 198. Girard, J. et al.: Glucose homeostasis in pregnancy and lactation. *Biochem Soc Trans*, 15:1028-1030, 1987.
 199. Girija, A. et al.: Influence of dietary supplementation during pregnancy on lactation performance. *J Trop Pediatrics*, 30:79-83, 1984.
 200. Godfrey, K.M. et al.: Neutral amino acid uptake by the microvillous plasma

- membrane of the human placenta is inversely related to fetal size at birth in normal pregnancy. *J Clin Endocrinol Metab*, 83:3320-3326, 1998.
201. Goldberg, G.R., et al.: Critical evaluation of energy intake data using fundamental principles of energy physiology. I. Deviation of cut-off values to identify under-recording. *Eur J Clin Nutr*, 45:569-581, 1991.
202. Goldberg, G.R. et al.: Longitudinal assessment of energy expenditure in pregnancy by the doubly-labelled water method. *Am J Clin Nutr*, 57:494-505, 1993.
203. Goldestein, J. & Tsuang, M. (Eds.): Gender and schizophrenia. *Schizophr Bull*, 16:179-344, 1990.
204. Goldman, H.I. et al.: Late effects of early dietary protein intake on low-birth-weight infants. *J Pediatrics*, 90:764-769, 1977.
205. Goodlin, R.C.: Do concepts of causes and prevention of cerebral palsy require revision? *Am J Obstet Gynecol*, 172:1830-1836, 1995.
206. Gormican, A. & Shrout, S.: Maternal nutritional status and retardation in offspring. *Postgrad Med*, 58:166-169, 1975.
207. Gortmaker, S.L.: The effects of prenatal care upon the health of the newborn. *Am J Public Health*, 69:653-660, 1979.
208. Grand R.J. et al.: The immature intestine: implications for nutrition of the neonate. *Ciba Found Symp*, 70:293-311, 1979.
209. Gray, M.J.: Hypertensive diseases in pregnancy. In: Onesti, G. et al. (Eds.): *Hypertension: Mechanisms and management*. New York: Grune & Stratton, 1973.
210. Gregory, P.B. & Rush, D.: Iatrogenic caloric restriction in pregnancy and birth weight. *Am J Perinatol*, 4:365-371, 1987.
211. Grieve, J.F.K.: Prevention of gestational failure by high protein diet. *J Reprod Med*, 13:170-174, 1974.
212. Grieve, J.F.K.: The prevention of gestational failure by antenatal diet control and planned surgical induction of parturition with special reference to EPH-gestosis. In: Rippmann, E.T. et al.: *Progress in EPH-gestosis*. 1975, Organization Gestosis-Press, 1975, pp. 133-140.
213. Grieve, J.F.K., et al.: Dieting in pregnancy: A study of the effect of a high protein low carbohydrate diet on birthweight in an obstetric population. In: Sutherland, HW & Stowers, T.M.: *Carbohydrate metabolism in pregnancy and the newborn*. Berlin-Heidelberg-New York: Springer-Verlag, pp. 518-534.
214. Gruenwald, P.: Chronic fetal distress and placental insufficiency. *Biol Neonat*, 5:215-265, 1963.
215. Gruenwald, P. et al.: Influence of environmental factors on foetal growth in man. *Lancet*, 1:1026-1029, 1967.
216. Gruenwald, P. & Minh, H.N.: Evaluation of body and organ weights in prenatal pathology. I. Normal standards derived from autopsies. *Am J Clin Pathol*, 34:247-253, 1960.
217. Gunther, M. & Stanier, J.: *Spec Rep Ser Med Res Coun*, No. 275, 1951, HMSO, London. (Cited by Widdowson [560])
218. György, P.: Biochemical aspects. In: Jelliffe, D.B. & Jelliffe, E.F.P.: The uniqueness of human milk (Symposium). *Amer J Clin Nutr*, 24:970-975, 1971.

219. Habicht, J.P. et al.: Relation of maternal supplementary feeding during pregnancy to birth weight and other sociobiological factors. In: Winick, M. (Ed.): *Nutrition and fetal development*. New York: John Wiley & Sons, 1974.
220. Halberg, F. et al.: From biologic rhythms to chronomes relevant for nutrition. In: Marriott, B.M.: *Not eating enough; Overcoming underconsumption of military operational rations*. National Academy Press, Washington, D.C., 1995, pp. 361-372.
221. Hales, C.N. et al.: Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ*, 303:1019-1022, 1991.
222. Hallack, M. et al.: Fetal rat brain damage caused by maternal seizure activity: prevention by magnesium sulfate. *Am J Obstet Gynecol*, 181:828-834, 1999.
223. Hamlin, R.H.J.: The prevention of eclampsia and pre-eclampsia. *Lancet*, 1:64-68, 1952.
224. Hamlin, R.H.J.: Prevention of pre-eclampsia. *Lancet*, 1:864-865, 1962.
225. Hammond, J.: Physiological factors affecting birth weight. *Proc Nutr Soc*, 2:8-14, 1944.
226. Handwerger, S. & Freemark, M.: Role of placental lactogen and prolactin in human pregnancy. In: Mahesh, V.B., et al.: Regulation of ovarian and testicular function. *Adv Exper Med Biol*, 219:399-420, 1987.
227. Harden, B.: The clinical management of pre-eclampsia and eclampsia. *Penna Med J*, 40:835-837, 1937.
228. Hardy, J.B.: Birth weight and subsequent physical and intellectual development. *New Engl J Med*, 289:973-974, 1973.
229. Hardy, J.B. et al.: *The first year of life*. Baltimore & London: Johns Hopkins University Press, 1979, 336 pp.
230. Harper, P.A. et al.: Neurological and intellectual status of prematures at 3 to 5 years of age. *J Pediatr*, 55:679-690, 1959.
231. Harper, P.A. & Wiener, G.: Sequelae of low birth weight. *Annu Rev Med*, 16:405-420, 1965.
232. Hassink, S.G. et al.: Serum leptin in children with obesity: Relationship to gender and development. *Pediatrics*, 98:201-203, 1996.
233. Hatjis C.G. & Meis P.J.: Total parenteral nutrition in pregnancy. *Obstet Gynecol*, 66:585-589, 1985.
234. Havel, R.J.: Caloric homeostasis and disorders of fuel transport. *New Eng J Med*, 287:1186-1192, 1972.
235. Hay, W.W., Jr., et al.: Effect of high levels of insulin on glucose utilization and glucose production in pregnant and non-pregnant sheep. *Proc Soc Exp Biol Med*, 189:275-284, 1988.
236. Hay, W.W., Jr.: Placental transport of nutrients to the fetus. *Horm Res*, 42:215-222, 1994.
237. Haymond, M.W. et al.: Increased gluconeogenic substrates in the small-for-gestational-age infant. *N Engl J Med*, 291:322-328, 1974.
238. Hellin, D.: Die Ursache der Multiparität der uniparen Tiere überhaupt und der Zwillingsschwangerschaft beim Menschen insbesonderer, München, 1985.
239. Hepner, R. & Bowen, M.: The placenta and fetus. *JAMA*, 172:427-432, 1960.

240. Hertzig, M. et al.: Intellectual levels of school children severely malnourished during the first two years of life. *Pediatr*, 49:814-824, 1972.
241. Hibbard, L.: Maternal mortality due to acute toxemia. *Obstet Gynecol* 42:263-270, 1973.
242. Higgins, A.C. et al.: Impact of the Higgins nutrition intervention program on birth weight: A within-mother analysis. *J Am Diet Assoc*, 89:1097-1103, 1989.
243. Higgs, S.C. et al.: A study of the plasma free amino acids in infants of low birth weight, with a comparison of oral feeding with milk and total parenteral nutrition. *S Afr Med J*, 51:5-9, 1977.
244. Hogue, C.J.R. et al.: Overview of the National Infant Mortality Surveillance (NIMS) Project – design, methods, results. *Public Health Rep*, 102:126-138, 1987.
245. Holmes, R.P. et al.: A prospective study of maternal serum insulin-like growth factor-I in pregnancies with appropriately grown or growth restricted fetuses. *Brit J Obstet Gynecol*, 105:1273-1278, 1998.
246. Hoorweg, J. & Stanfield, J.P.: The effects of protein energy malnutrition on intellectual and motor abilities in later childhood and adolescence. *Develop Med Child Neurol*, 18:330-350, 1976.
247. Howard, R.C. et al.: Studies of babies born at high altitude. II. Measurement of birth weight, body length, and head size. *Am J Dis Child*, 93:670-674, 1957.
248. Howard, R.C. et al.: Studies of babies born at high altitude. III. Arterial oxygen saturation and hematocrit values at birth. *Am J Dis Child*, 93:674-678, 1957.
249. Huffman, S.L. et al.: Postpartum amenorrhea: how is it affected by maternal nutritional status. *Science*, 200:1155-1157, 1978.
250. Hughes, E.C., (Ed.): *Obstetric-Gynecologic Terminology*, Report of The Committee on Terminology of the American College of Obstetricians and Gynecologists. Philadelphia: F.A. Davis, 1972, pp. 422-423.
251. Hunt, I.F. et al.: Effect of nutrition education on the nutritional status of low-income pregnant women of Mexican descent. *Am J Clin Nutr*, 29:675-684, 1976.
252. Hunt, I.F. et al.: Zinc supplementation during pregnancy: Effects on selected blood constituents and on progress and outcome of pregnancy in low-income women of Mexican descent. *Am J Clin Nutr*, 40:508-521, 1984.
253. Hurley, R.: *Poverty and mental retardation: A causal relationship*. New York: Random House, 1970, from Wylie, B.: The challenge of infant mortality. *Bull Cleveland Acad Med*, June 1965.
254. Hurley, T.W. et al.: Differential effects of placental lactogen, growth hormone and prolactin on rat liver ornithine decarboxylase activity in the perinatal period. *Life Sciences*, 27:2269-2275, 1980.
255. Hutchinson, D.L. et al.: The total body water and the water turnover in pregnancy studied with deuterium oxide as isotopic tracer. *J Clin Invest*, 33:235-241, 1954.
256. Hytten, F. & Leitch, I.: *The physiology of human pregnancy*, 2nd ed. London: Blackwell Science Publishers, 1971.
257. Iyenger, L.: Effects of dietary supplements late in pregnancy on the expectant mother and her newborn. *Ind J Med Res*, 55:85-89, 1967.

258. Iyenger, L.: Urinary estrogen excretion in undernourished pregnant Indian women. *Am J Obstet Gynecol*, 102:834-838, 1968.
259. Jacobson, H.N. & Mills, S.H.: Pregnant and lactating women. In: Mayer, J (Ed): Nutrition policies in the 70's. San Francisco: W.H. Freeman, 1973, from President's Panel on Mental Retardation: *National Action to Combat Mental Retardation*. Washington, D.C., U.S. Government Printing Office, 1962.
260. Jacobson, M.: *Developmental neurobiology*, 3rd ed. New York: Plenum Press, 1991, pp. 237-250, 285-293.
261. Jain, M.L. & Garg, A.K.: Burns with pregnancy – a review of 25 cases. *Burns*, 19:166-167, 1993.
262. James, S.A.: Racial and ethnic differences in infant mortality and low birth weight. A psychosocial critique. *Ann Epidemiol*, 3:130-136, 1993.
263. Jansen, A.A. et al.: Quantity and composition of breast milk in Biak Island (Netherlands New Guinea). *Trop Geog Med*, 12:138-144, 1960.
264. Jauniaux, E. et al.: Free amino acid distribution inside the first trimester human gestational sac. *Early Hum Dev*, 51:159-169, 1998.
265. Jauniaux, E. et al.: Free amino acids in human fetal liver and fluids at 12-17 weeks of gestation. *Hum Reprod*, 14:1638-1641, 1999.
266. Jeans, P.C. et al.: Incidence of prematurity in relation to maternal nutrition. *J Am Diet Assoc*, 31:576-581, 1955.
267. Jelliffe, D.B.: Unique properties of human milk. Remarks on some recent developments. *J Reprod Med*, 14:133-137, 1975.
268. Jelliffe, B.D. & Jelleffe, E.F.P.: The uniqueness of human milk. *Am J Clin Nutr*, 24:967-1024, 1971.
269. Jennings, J.: Diet and the hormones of pregnancy. *Prevention*, December 1972, pp 103-125.
270. Johnstone, F.D., et al.: Nitrogen retention in pregnancy. *J Obstet Gynaecol Brit Commonw*, 79:777-781, 1972.
271. Josephson, M.A. et al.: Pregnancy in a nonimmunosuppressed transplant recipient. *Am J Kidney Dis*, 32:661-663, 1998.
272. Kalhan, S.C.: Protein and nitrogen metabolism in gestational diabetes. *Diabetes Care*, 21(Supp 2):B75-B78, 1998.
273. Kalil, R.E.: Synapse formation in the developing brain. *Sci Amer*, 261:6:76-85, 1989 (December).
274. Kalkhoff, R.K. et al.: Relative effects of pregnancy, human placental lactogen and prednisolone on carbohydrate tolerance in normal and subclinical diabetic subjects. *Diabetes*, 18:153-175, 1969.
275. Kaminetzky, H. et al.: The effect of nutrition in teen-age gravidae on pregnancy and the status of the neonate. *Am J Obstet Gynecol*, 115:639-646, 1973.
276. Kaplan, M. et al.: Fasting and the precipitation of labor: The Yom Kippur effect. *J Amer Med Assoc*, 250:1317-1318, 1983.
277. Kawi, A.A. & Pasamanick, B.: Association of factors of pregnancy with reading disorders in childhood. *JAMA*, 166:1420-1423, 1958.
278. Kelman, L. et al.: Effects of dietary protein restriction on albumin synthesis, albumin catabolism, and the plasma aminogram. *Am J Clin Nutr*, 25:1174-1178,

- 1972.
279. Kennaugh, J.M. & Hay, W.W., Jr.: Nutrition of the fetus and newborn. *West J Med*, 147:435-448, 1987.
280. Kennaugh, J.M. et al.: Ontogenetic changes in protein synthesis rate and leucine oxidation rate during fetal life. *Pediat Res*, 22:688-692, 1987.
281. Kennedy, D.: Small systems of nerve cells. *Sci Amer*, 216(May):44-52, 1967.
282. Kelts, D.G. et al.: Studies on requirements for amino acids in infants with disorders of amino acid metabolism. *Pediat Res*, 19:86-91, 1985.
283. Kim, Y.J. & Felig, P.: Maternal and amniotic fluid substrate levels during caloric deprivation in human pregnancy. *Metabolism*, 21:507-512, 1972.
284. King J.C. et al.: Nitrogen retention, total body ^{40}K and weight gain in teenage pregnant girls. *J Nutri*, 103:772-785, 1973.
285. Kinsey, V.E. et al.: PaO_2 levels and retrosternal fibroplasia: A report of the cooperative study. *Pediatrics*, 60:655-668, 1977.
286. Kitay, D.: Dysfunctional antepartum nutrition. *J Reprod Med*, 7:251-256, 1971.
287. Kjeldsen, J. & Pedersen, J.: Relation of residual placental blood-volume to onset of respiration and the respiratory-distress syndrome in infants of diabetic and non-diabetic mothers. *Lancet*, 1:180-184, 1967.
288. Knobloch, H. et al.: Neuropsychiatric sequelae of prematurity: A longitudinal study. *JAMA*, 161:581-585, 1956.
289. Knobloch, H. & Pasamanick, B.: Seasonal variation in the births of the mentally deficient. *Am J Public Health*, 48:1201-1208, 1958.
290. _____: Prematurity and development. *J Obstet Gynecol Br Commonw*, 66:729-731, 1959.
291. _____: Distribution of intellectual potential in infant population. In: Pasamanick, B.: *The epidemiology of mental disorder*. American Association for the Advancement of Science, 1959.
292. _____: Mental subnormality. *New Engl J Med*, 266:1045-1051, 1092-1097, and 1155-1161, 1962.
293. _____: The developmental behavioral approach to the neurologic examination in infancy. *Child Dev*, 33:181-198, 1962.
294. _____: Prospective studies on the epidemiology of reproductive casualty: Methods, findings, and some implications. *Merrill-Palmer Q. Behav & Dev*, 12:27-43, 1966.
295. _____: Prediction from the assessment of neuromotor and intellectual status in infancy. In: Zunin, J. & Jervis, G.: *Psychopathology of mental development*. New York: Grune & Stratton, 1967.
296. Kowarski, A.A. et al.: Plasma concentration of aldosterone in normal subjects from infancy to adulthood. *J Clin Endocrinol Metab*, 38:489-491, 1974.
297. Kraus, G. et al.: Prophylactic use of hydrochlorothiazide in pregnancy. *JAMA*, 198:128-132, 1966.
298. Krigman, M.R. & Hogan, E.L.: Undernutrition in the developing rat: effect on myelination. *Brain Res*, 107:239-255, 1976.
299. Kugelmas, I.N. et al.: Nutritional improvement of child mentality. *Am J Med Sci*, 208:631-633, 1944.

300. Kupferminc, M.J. et al.: Tumor necrosis factor-alpha is elevated in plasma and amniotic fluid in patients with severe pre-eclampsia. *Am J Obstet Gynecol*, 170:1752-1757, 1994.
301. _____: Immunoreactive tumor necrosis factor-alpha is elevated in maternal plasma but undetected in amniotic fluid in the second trimester. *Am J Obstet Gynecol*, 171:976-979, 1994.
302. Kuruvilla, A.G. et al.: Altered activity of the system AA amino acid transporter in microvillous membrane vesicles from placentas of macrosomic babies born to diabetic women. *J Clin Invest*, 94:689-695, 1994.
303. Kusin, J.A. et al.: Chronic undernutrition in pregnancy and lactation. *Proc Nutr Soc*, 52:19-28, 1993.
304. Kuzniar, J. et al.: Echocardiographic estimation of hemodynamics in hypertensive pregnancy. *Am J Obstet Gynecol*, 144:430-437, 1982.
305. La Gasse, L.L. et al.: Interpreting research on prenatal substance exposure in the context of multiple confounding factors. *Clin Perinatol*, 26:39-54, 1999.
306. Langhoff-Roos, J. et al.: Placental hormones and maternal glucose metabolism. A study of fetal growth in normal pregnancy. *Br J Obstet Gynecol*, 96:320-326, 1989.
307. Langlois, P.L.: The size of the normal uterus. *J Reprod Med*, 4:220-228, 1970.
308. Lazer, S. et al.: Complications associated with the macrosomic fetus. *J Reprod Med*, 31:501-505, 1986.
309. Lechtig, A. et al.: Nutrición materna y crecimiento fetal. *Archivos Latinoamer Nutr*, 21:505-530, 1971.
310. Lechtig, A. et al.: Influencia de la nutrición materna sobre el crecimiento fetal en poblaciones rurales de Guatemala. I. Aspectos dietéticos. *Archivos Latinoamer Nutr*, 22:101-105, 1972.
311. Lechtig, A. et al.: Influencia de la nutrición materna sobre el crecimiento fetal en poblaciones rurales de Guatemala. II. Suplementación alimentaria. *Archivos Latinoamer Nutr*, 22:117-131, 1972.
312. Lechtig, A. et al.: Effect of moderate maternal malnutrition on the placenta. *Am J Obstet Gynecol*, 123:191-201, 1975.
313. Lechtig, A. et al.: Effect of food supplementation during pregnancy on birth weight. *Pediatrics*, 56:508-520, 1975.
314. Lederman, S.A. & Rosso, P.: Effects of fasting during pregnancy on maternal and fetal weight and body composition in well-nourished and undernourished rats. *J Nutr*, 111:1823-1832, 1981.
315. Lee, R.V. et al.: Total parenteral nutrition during pregnancy. *Obstet Gynecol*, 68:563-571, 1986.
316. Le Magnen, J.: Body energy balance and food intake: a neuroendocrine regulatory mechanism. *Physiol Rev*, 63:314-386, 1983.
317. Lemons, J.A. & Schreiner, R.L.: Amino acid metabolism in the ovine fetus. *Am J Physiol*, 244:E459-E466, 1983.
318. Lepercq, J. et al.: Overexpression of placental leptin in diabetic pregnancy: A critical role for insulin. *Diabetes*, 47:847-850, 1998.
319. Lepercq, J. et al.: Macrosomia revisited: Ponderal index and leptin delineate

- subtypes of fetal overgrowth. *Am J Obstet Gynecol*, 181:621-625, 1999.
320. Leturque, A., et al.: Glucose metabolism in pregnancy. *Biol Neonat*, 51:64-69, 1987.
321. Leverton, R.M. & Gram, M.R.: Nitrogen excretion of women related to the distribution of animal protein in daily meals. *J Nutr*, 39:57-65, 1949.
322. Lewin, R.: Starved brains: A generation of clumsy, feeble-minded millions. *Psychol Today*, September 1975.
323. Lewis, P.D. et al.: Effect of undernutrition on cell generation in the rat hippocampus. *Brain Research*, 168:186-189, 1979.
324. Li, D.K. et al.: Periconceptional multivitamin use in relation to the risk of congenital urinary tract anomalies. *Epidemiology*, 6:212-218, 1995.
325. Liang, P.H. et al.: Evaluation of mental development in relation to early malnutrition. *Am J Clin Nutr*, 20:1290-1294, 1967.
326. Lichy, J.A. et al.: Studies of babies born at high altitude. I. Relation of altitude to birth weight. *Am J Dis Child*, 93:666-669, 1957.
327. Liechty, E.A. et al.: Effects of circulating IGF-1 on glucose and amino acid kinetics in the ovine fetus. *Am J Physiol*, 271:E177-E185, 1996.
328. Light, I.J., et al.: Maternal intravenous glucose administration as a cause of hypoglycemia in the infant of the diabetic mother. *Am J Obstet Gynecol*, 113:345-350, 1972.
329. Lilienfeld, A.M. & Parkhurst, E.: A study of the association of factors of pregnancy and parturition with the development of cerebral palsy. *Am J Hyg*, 53:262-282, 1951.
330. Lilienfeld, A.M. & Pasamanick, B.: Association of maternal and fetal factors with the development of epilepsy. I. Abnormalities in the prenatal and para-natal periods. *J Am Med Assoc*, 155:719-724, 1954.
331. Lin, T.J. et al.: Progesterone production rates during the third trimester of pregnancy in normal women, diabetic women, and women with abnormal glucose tolerance. *J Clin Endocrinol Metab*, 34:287-297, 1972.
332. Lindblad, B.S. & Rahimtoola, R.J.: A pilot study of the quality of human milk in a lower socio-economic group in Karachi, Pakistan. *Acta Paediat Scand*, 63:125-128, 1974.
333. Lindheimer, M. & Katz, A.: Sodium and diuretics in pregnancy. *New Engl J Med*, 288:891-894, 1973.
334. Little, W.J.: On the influence of abnormal parturition, difficult labor, premature birth, and asphyxia neonatorum on the mental and physical conditions of the child, especially in relation to deformities. *Trans Obstet Soc London*, 3:293-344, 1862.
335. Livingstone, M.B.E. et al.: Accuracy of weighed dietary records in studies of diet and health. *Br Med J*, 300:708-712, 1990.
336. LoIudice, T.A. et al.: Pregnancy and jejunointestinal bypass: Treatment of complications with total parenteral nutrition. *South Med J*, 73:256-258, 1980.
337. Long, P.A. et al.: Importance of abnormal glucose tolerance (hypoglycaemia and hyperglycaemia) in the aetiology of pre-eclampsia. *Lancet*, 1:923-925, 1977.
338. Longo, L.D.: Disorders of placental transfer. In: Assali, NS: Pathophysiology

- of gestation, Vol 2. New York: Academic Press, 1972, pp 1-76.
339. Longo, L.D.: Maternal blood volume and cardiac output during pregnancy: A hypothesis of endocrinologic control. *Am J Physiol*, 245:R720-R729, 1983.
340. Lowe, C.U.: Research in infant nutrition: The untapped well. *Am J Clin Nutr*, 25:245-254, 1972.
341. Loy, G.L. et al.: Feto-placental deamination and decarboxylation of leucine. *Am J Physiol*, 259:E492-E497, 1990.
342. Lubchenco, L.O. et al.: Sequelae of premature birth: Evaluation of premature infants of low birth weight at ten years of age. *Am J Dis Child*, 106:101-115, 1972.
343. Lubchenco, L.O. et al.: Neonatal mortality rate: Relationship to birthweight and gestational age. *J Pediatr*, 81:814-822, 1972.
344. Lucey, J.F.: Hyperbilirubinemia of prematurity. *Pediatr*, 25:690-710, 1960.
345. Lusk W.T.: The science and art of midwifery. New York: D Appleton & Co, 1890.
346. MacGillivray, I: Pre-eclampsia: The hypertensive disease of pregnancy. London: WB Saunders Company, Ltd, 1983, p. 39.
347. Machlin, L.J., & Bendich, A.: Free radical tissue damage: protective role of antioxidant nutrients. *FASEB J*, 1:441-445, 1987.
348. MacLean, W.C. & Graham, G.G.: The effect of energy intake on nitrogen content of weight gained by recovering malnourished infants. *J Clin Nutr*, 33:903-909, 1980.
349. Macy, I.G. & Kelly, H.J.: In: Kon, S.K. & Cowie, A.T.: Milk: *The mammary gland and its secretion*. New York: Academic Press, 1961, p. 265.
350. Maeck, J.V.S. & Strausfeld, K.: Analgesia and anesthesia in premature labor. *Clin Obstet Gynec*, 7:707-732, 1964.
351. Main, A.N.H. et al.: Intravenous feeding to sustain pregnancy in patient with Crohn's disease. *Br Med J*, 283:1221-1222, 1981.
352. Malandro, M.S. et al.: Effect of low-protein diet-induced intrauterine growth retardation on rat placental amino acid transport. *Am J Physiol*, 271:C295-C303, 1996.
353. Manchester, W.: American Caesar: *Douglas MacArthur 1880-1964*. Boston-Toronto: Little, Brown and Company, 1978, p. 465.
354. Manocha, S.L. & Olkowski, Z.L.: Experimental protein malnutrition in primates – cytochemistry of the nervous system. *Am J Phys Anthropol*, 38:439-446, 1973.
355. Manocha, S.L. & Sharma, S.P.: Nucleolar activity in the primate dorsal root ganglion cells associated with dietary protein malnutrition. *Acta Anat*, 100:68-77, 1978.
356. Manocha, S.L. & Sharma, S.P.: Lipofuscin accumulation in squirrel monkey spinal cord consequent to protein malnutrition during gestation. *Experientia*, 34(Part 1):377-379, 1978.
357. Manocha, S.L.: *Malnutrition and retarded human development*. Springfield, IL: Charles C Thomas, 1972, p 182.
358. Markand, O.N. et al.: Nonketotic hyperglycinemia: Electroencephalographic and evoked potential abnormalities. *Neurology*, 32:151-156, 1982.

359. Marriott, B.M. (Ed.): Not eating enough: Overcoming underconsumption of military operational rations. National Academy Press, 1995, Washington, 483 p.
360. McGanity, W.J. et al.: The Vanderbilt cooperative study of maternal and infant nutrition. V. Description and outcome of obstetric sample. *Am J Obstet Gynecol*, 67:491-500, 1954.
361. McGanity, W.J. et al.: The Vanderbilt cooperative study of maternal and infant nutrition. VI. Relationship of obstetric performance to nutrition. *Am J Obstet Gynecol*, 67:501-527, 1954.
362. McGanity, W.J. et al.: The Vanderbilt cooperative study of maternal and infant nutrition. XII. Effect of reproduction cycle on nutritional status and requirements. *JAMA*, 168:2138-2145, 1958.
363. Mednick, S.A. et al.: Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiat*, 45:189-192, 1988.
364. Mellanby, E.: Nutrition and child-bearing. *Lancet*, 2:1131-1137, 1933.
365. Mellor, D.J. & Mathesson, I.C.: Daily changes in the curved crown-rump length of individual sheep fetuses during the last 60 days of pregnancy and effects of different levels of maternal nutrition. *Quart J Exp Physiol*, 64:119-131, 1979.
366. Mengert, W. & Tacchi, D.: Pregnancy toxemia and sodium chloride. *Am J Obstet Gynecol*, 81:601-605, 1961.
367. Menon, R.K. et al.: Transplacental passage of insulin in pregnant women with insulin-dependent diabetes mellitus. *New Eng J Med*, 323:309-315, 1990.
368. Menzies, D.S. & Prystowsky, H.: Acute hemorrhagic pancreatitis during pregnancy and the puerperium associated with thiazide therapy. *J Fla Med Assoc*, 54:564-565, 1967.
369. Mestyán, J. & Járai, I.: Neonatal anthropometry: its value in the assessment of nutritional status and neonatal blood homeostasis. *Acta Paediatr Acad Scien Hungar*, 22:49-69, 1981.
370. Mestyán, J. et al.: Hyperaminoacidemia due to the accumulation of gluconeogenic amino acid precursors in hypoglycemic small-for-gestational-age infants. *J Pediat*, 87:409-414, 1975.
371. Metcoff, J. et al.: Effect of food supplementation (WIC) during pregnancy on birth weight. *Am J Clin Nutr*, 41:933-947, 1985.
372. Metzger, B.E. & Freinkel, N.: Accelerated starvation in pregnancy: Implications for dietary treatment of obesity and gestational diabetes mellitus. *Biol Neonat*, 51:78-85, 1987.
373. Miller, F.C. et al.: The effect of maternal blood sugar levels on fetal activity. *Obstet Gynecol*, 52:662-665, 1978.
374. Miller, H.C. & Jekel, J.F.: Associations between unfavorable outcomes in successive pregnancies. *Am J Obstet Gynec*, 153:20-24, 1985.
375. Miller, V. et al.: Impact of the WIC program on the iron status of infants. *Pediatrics*, 75:100-105, 1985.
376. Milstien, S. et al.: Hyperphenylalaninemia due to dihydropteridine reductase deficiency. *J Pediat*, 89:763-766, 1976.

377. Minkowitz, S. et al.: Fatal hemorrhagic pancreatitis following chlorothiazide administration in pregnancy. *Obstet Gynecol*, 24:337-342, 1964.
378. Mitchell, J. et al.: Dietary habits of a group of severe pre-eclamptics in Alabama. *J Natl Med Assoc*, 41:122-125, 1949.
379. Moe, N.: The deposits of fibrin and fibrin-like materials in the basal plate of the normal human placenta. *Acta Pathol Microbiol Scand*, 75:1-17, 1969.
380. Moe, N.: Histological and histochemical study of the extracellular deposits in the normal human placenta. *Acta Pathol Microbiol Scand*, 76:419-431, 1969.
381. Moe, N.: Deposits of fibrin and plasma proteins in the normal human placenta. *Acta Pathol Microbiol Scand*, 76:74-88, 1969.
382. Monge, C.: *Acclimatization in the Andes: Historical confirmations of climatic aggression in the development of Andean man*. Baltimore: Johns Hopkins Press, 1948.
383. Mönckeberg, F.: Effect of early marasmic malnutrition on subsequent physical and psychological development. In: Scrimshaw, N.S. & Gordon, J.E.: *Malnutrition, learning and behavior*, Vol. 10. Cambridge, MA: MIT Press, Cambridge, 1968, pp. 269-278.
384. Moore, F.D. et al.: *The body cell mass and its supporting environment*. Philadelphia: WB Saunders, 2964, pp. 532-535.
385. Morris, F.H. et al.: Effects of fasting on uterine blood flow and substrate uptake in the sheep. *J Nutr*, 110:2433-2443, 1980.
386. Morgane, P.J., et al.: The effect of protein malnutrition on the developing central nervous system of the rat. *Neurosci Biobehav Rev*, 2:137-230, 1978.
387. Moustgaard, J.: Nutritive influences upon reproduction. *J Reprod Med*, 7:275-280, 1971; *J Reprod Med* 8:1-12, 1972.
388. Muirhead, E.E. et al.: Persistent hypotension associated with hypermedullipinemia: a new syndrome. *Blood Pressure*, 7:138-148, 1992.
389. Muirhead, E.E.: personal communication.
390. Myrianthopoulos, N.C.: Congenital malformations in twins: epidemiologic survey. *Birth Defects*, 11:1-39, 1975.
391. Naeye, R.L. et al.: Effects of maternal nutrition on the human fetus. *Pediatrics*, 52:494-503, 1973.
392. Naeye, R.L., et al.: Abruptio placentae and perinatal death: a prospective study. *Am J Obstet Gynec*, 128:740-746, 1977.
393. Naismith, D.J.: The requirement for protein, and the utilization of protein and calcium during pregnancy. *Metabolism*, 15:582-595, 1966.
394. _____: The foetus as a parasite. *Proc Nutr Soc*, 28:25-31, 1969.
395. Nei, M. et al.: A maternal complex partial seizure in labor can affect fetal heart rate. *Neurology*, 51:904-906, 1998.
396. Nelson, K.B. & Ellenberg, J.H.: Maternal seizure disorder, outcome of pregnancy, and neurologic abnormalities in the children. *Neurology*, 32:1247-1254, 1982.
397. Ness, R.B. et al.: Cocaine and tobacco use and the risk of spontaneous abortion. *New Eng J Med*, 340:333-339, 1999.

398. Neville, M.C. et al.: Endocrine regulation of nutrient flux in the lactating woman. In: Allen, L. et al.: *Nutrient regulation during pregnancy, lactation, and infant growth*. New York: Plenum, 1994, pp 86-87.
399. Nicholl, R.A.: The coupling of neurotransmitter receptors to ion channels in the brain. *Science*, 241:545-551, 1988.
400. Nichols, B.L. & Nichols, V.N.: Nutritional physiology in pregnancy and lactation. *Adv Pediatrics*, 30:473-515, 1983.
401. Nielsen, P.V. et al.: Absence of human placental lactogen in an otherwise uneventful pregnancy. *Am J Obstet Gynecol*, 135:322-326, 1979.
402. Niswander, K.R. & Gordon, M.: *The women and their pregnancies*. US Department of Health, Education, and Welfare. Philadelphia: WB Saunders, 1972, 540 p.
403. Noback, C.R. & Eisenman, L.M.: Some effects of protein-calorie under-nutrition on the developing central nervous system of the rat. *Anat Rec*, 201:67-73, 1981.
404. Ono, T., et al.: Neural mechanisms of feeding behavior. In: Katsuki, Y., et al.: *Brain mechanisms of sensation*. New York: John Wiley, 1981, pp. 271-286.
405. Orten, J.M. & Neuhaus, O.W.: *Human biochemistry*, 9th ed. St. Louis, MO: C.V. Mosby, 1975, pp. 313-315.
406. O'Sullivan, J.B.: Diabetes mellitus after GDM. *Diabetes*, 40(Supp 2):131-135, 1991.
407. Papageorgious, A.N. et al.: Specialized perinatal care: Impact on perinatal mortality. *Can Med Assoc J*, 116:506-507, 1977.
408. Parker, J.D. et al.: Associations between measures of socioeconomic status and low birth weight, small for gestational age, and premature delivery in the United States. *Ann Epidemiol*, 4:271-278, 1994.
409. Pasamanick, B.: The life and death sciences: Uses and abuses of epidemiology. The Rema Lapouse Gold Medal Lecture. *Am Pub Health Assoc*, November 2, 1977, Washington, D.C.
410. Pasamanick, B. et al.: Socioeconomic status and some precursors of neuropsychiatric disorder. *Am J Orthopsychiatry*, 26:595-601, 1956.
411. Pasamanick, B. & Knobloch, H.: Seasonal variation in complications of pregnancy. *Obstet Gynecol*, 12:110-112, 1958.
412. _____: Seasonal variation in the births of the mentally deficient - A reply. *Am J Pub Health*, 50:1737-1742, 1960.
413. _____: The epidemiology of reproductive casualty. In: VanKrevalen, D.A.: *Child psychiatry and prevention*. Berne: Huber, 1964.
414. _____: Retrospective studies on the epidemiology of reproductive casualty: Old and new. *Merrill-Palmer Q Behav & Dev*, 12:7-26, 1966.
415. Pasamanick, B. & Lilienfeld, A.M.: Association of maternal and fetal factors with development of mental deficiency. I. Abnormalities in the prenatal and paranatal periods. *JAMA*, 159:155-160, 1955.
416. Pedersen, J.: Weight and length at birth of infants of diabetic mothers. *Acta Endocrin*, 16:330-342, 1954.

417. Pelletier, D.L. et al.: Epidemiologic evidence for a potentiating effect of malnutrition on child mortality. *Am J Public Health*, 83:1130-1133, 1993.
418. Pencharz, P.B. et al.: Total-body protein turnover in human premature neonates: effects of birth weight, intrauterine nutritional status and diet. *Clin Sci*, 61:207-215, 1981.
419. Pike, R.L.: Sodium intake during pregnancy. *J Am Diet Assoc*, 44:176-181, 1964.
420. Pike, R.L. & Gursky, D.S.: Further evidence of deleterious effects produced by sodium restriction during pregnancy. *Am J Clin Nutr*, 23:883-889, 1970.
421. Pike, R.L. & Smiciklas, H.A.: A reappraisal of sodium restriction during pregnancy. *Int J Gynaecol Obstet*, 10:1-8, 1972.
422. Platt, B.S. & Stewart, R.J.C.: Reversible and irreversible effects of protein-calorie deficiency on the central nervous system of animals and man. In: Bourne, G.H. (Ed.), *World review of nutrition and dietetics*, Vol 13. Basel/NewYork: Karger, 1971, pp 43-85.
423. Plehwe, W.E., et al.: Outcome of pregnancy complicated by diabetes: Experience with 232 patients in a 4 year period. *Diabetes Res*, 1:67-78, 1984.
424. Pomerance, J.: Weight gain in pregnancy: How much is enough? *Clin Pediatr*, 11:554-556, 1972.
425. Poppitt, S.D. et al.: Energy-sparing strategies to protect human fetal growth. *Am J Obstet Gynec*, 177:118-125, 1994.
426. Pozefsky, T. et al.: Amino acid balance across the tissues of the forearm in postabsorptive man: effects of insulin at two dose levels. *J Clin Invest*, 48:2273-2282, 1969.
427. Prentice, A.M. et al.: Prenatal dietary supplementation of African women and birth-weight. *Lancet*, 1:489-492, 1983.
428. Prentice, A.M. et al.: Increased birthweight after prenatal dietary supplementation of rural African women. *Am J Clin Nutr*, 46:912-925, 1987.
429. Prentice, A.M.: Can maternal dietary supplements help in preventing infant malnutrition? *Acta Pediat Scand Suppl*, 374:67-77, 1991.
430. Prentice, A.M. et al.: Energy balance in pregnancy and lactation. In: Allen, L. et al.: Nutrient regulation during pregnancy, lactation, and infant growth. New York: Plenum, 1994, pp 11-26.
431. Primrose, T. & Higgins, A.: A study in antepartum nutrition. *J Reprod Med*, 7:257-264, 1971.
432. Pritchard, J.A. & MacDonald, P.C.: *Williams obstetrics*, 16th edition. New York: Appleton-Century-Crofts, 1980, pp. 639-644.
433. Rahman, S.A. et al.: Biosynthesis of proteins in human placentae from normal and toxæmic pregnancies. *J Reprod Fert*, 27:296-297, 1971 (abstract).
434. Rahman, S.A. et al.: In vitro biosynthesis of proteins in human placentae from normal and toxæmic pregnancies. *Acta Endocrin*, 73:567-576, 1973.
435. Räihä, N.C.R.: Biochemical basis for nutritional management of preterm infants. *Pediatrics*, 53:147-156, 1974.
436. Räihä, N.C.R. et al.: Milk protein quantity and quality in low-birth-weight infants. I. Metabolic responses and effects on growth. *Pediatrics*, 57:659-674, 1976.

437. Rassin, D.K. et al.: Milk protein quantity and quality in low-birth-weight infants. II. Effects on selected essential and non-essential amino acids in plasma and urine. *Pediatrics*, 59:407-422, 1977.
438. Rassin, D.K. et al.: Milk protein quantity and quality in low-birth-weight infants. IV. Effects on tyrosine and phenylalanine in plasma and urine. *J Pediatr*, 90:356-360, 1977.
439. Reece, E.A. et al.: Metabolic changes in diabetic and nondiabetic subjects during pregnancy. *Obstet Gynecol Survey*, 49:64-71, 1994.
440. Rehm, R.D. et al.: Prediction of the respiratory distress syndrome; by analysis of cord protein and alpha-1 antitrypsin. *Minn Med*, 57:443-447, 1974.
441. Reynolds, M.: Disorders of lactation and the mammary gland. In: Assali, N.S. and Brinkman, C.R.: *Pathophysiology of gestation*, Vol. 1. New York: Academic Press, 1972, pp. 550-553.
442. Richmond, S. et al.: The obstetric management of fetal distress and its association with cerebral palsy. *Obstet Gynecol*, 83:643-646, 1994.
443. Rider, R.V. et al.: Associations between premature births and socioeconomic status. *Am J Public Health*, 45:1022-1028, 1955.
444. Rinehart, B.K. et al.: Expression of the placental cytokines tumor necrosis factor α , interleukin 1 β , and interleukin 10 in pre-eclampsia. *Am J Obstet Gynecol*, 181:915-920, 1999.
445. Rizos, N. et al.: Natural history of placenta previa ascertained by diagnostic ultrasound. *Am J Obstet Gynecol*, 133:287-291, 1979.
446. Robertson, E.G.: The natural history of oedema during pregnancy. *J Obstet Gynaecol Br Commonw*, 78:520-529, 1971.
447. Robinson, C.H.: Fundamentals of normal nutrition, 2nd ed. New York: Macmillan, 1973, pp. 167-184
448. Robinson, M.: Salt in pregnancy. *Lancet*, 1:178-181, 1958.
449. Rogers, M.E. et al.: *Prenatal and paranatal factors in the development of childhood behavior disorders*. Copenhagen: Munksgaard, 1955.
450. Roht, L.H. et al.: The association of multiple induced abortions with subsequent prematurity and spontaneous abortion. *Acta Obstet Gynaec Jap*, 23:140-145, 1976.
451. Ronzoni, S. et al.: Umbilical amino acid uptake at increasing maternal amino acid concentrations: Effect of a maternal amino acid infusate. *Am J Obstet Gynecol*, 181:477-483, 1999.
452. Rosenbaum, A.L. et al.: Neuropsychologic outcome of children whose mothers had proteinuria during pregnancy. *Obstet Gynecol*, 33:118-123, 1969.
453. Rosenfeld, C.R. et al.: Effects of epinephrine on distribution of blood flow in the pregnant ewe. *Am J Obstet Gynec*, 124:156-163, 1976.
454. Rosenfeld, C.R. and West J.: Circulatory response to systemic infusion of norepinephrine in the pregnant ewe. *Am J Obstet Gynec*, 127:376-383, 1977.
455. Rosenstein, S.S.: *Traité Pratique des Maladies des Reins*. Paris: Adrein Delahaye, 1874.
456. Ross, R.: Relation of vitamin deficiency to the toxemia of pregnancy. *South Med J*, 28:120-122, 1935.

457. Ross, R.A.: Nutrition in maternal and perinatal morbidity and mortality in a rural state: 1930-1950. *J Reprod Med*, 7:245-250, 1971.
458. Ross, R.A. et al.: A study of certain dietary factors of possible etiologic significance in toxemias of pregnancy. *Am J Obstet Gynecol*, 35:426-440, 1938.
459. Rosso, P.: Maternal nutrition, nutrient exchange, and fetal growth. In: Winick, M.: *Nutritional disorders of American women*. New York: John Wiley & Sons, 1977, pp. 3-25.
460. Rosso, P.: Prenatal nutrition and fetal growth development. *Pediatric Annals*, 10:21-32, 1981.
461. Rosso, P. et al.: Hemodynamic changes in underweight pregnant women. *Obstet Gynecol*, 79:908-912, 1992.
462. Rosso, P. & Salas, S.P.: Mechanisms of fetal growth retardation in the underweight mother. In: Allen, L. et al.: *Nutrient regulation during pregnancy, lactation, and infant growth*. New York: Plenum, 1994, pp. 1-9.
463. Rothschild, M.A. et al.: Albumin metabolism. *Gastroenterology*, 64:324-337, 1973.
464. Rubin, R. et al.: Psychological and educational sequelae of prematurity. *Pediatr*, 52:352-363, 1973.
465. Rush, D.: The National WIC Evaluation, 1986 (undated), Vol. I, Summary, Research Triangle Institute, Research Triangle, N.C., Table II-1, p. II-3; Vol. III, p. IV-45.
466. Rush, D. et al.: The National WIC Evaluation: Evaluation of the Special Supplemental Food Program for Women, Infants, and Children. *Am J Clin Nutr*, 48(Supp):389-519, 1988.
467. Rush, D.: Testimony before the Joint Hearing, Select Committee on Hunger, House of Representatives, and the Committee on Agriculture, Nutrition, and Forestry, United States Senate, 101st Congress, second session, January 24, 1990, pp. 33-41, 171-180.
468. Ryan, A.S. et al.: The effect of the WIC program on nutrient intakes of infants, 1984. *Med Anthropol*, 9:153-172, 1985.
469. Sacks, D.A., et al.: When is fasting really fasting? The influence of time of day, interval after a meal, and maternal body mass on maternal glycemia in gestational diabetes. *Am J Obstet Gynecol*, 181:904-911, 1999.
470. Samaan, N. et al.: Metabolic effects of placental lactogen (HPL) in man. *J Clin Endocrinol Metab*, 28:485-491, 1968.
471. Sammour, M.B. et al.: Creatine phosphokinase activity in maternal, cord blood and placentas of normal pregnancy, and in EPH-gestosis. In: Rippmann, E.T. et al.: *Progress in EPH-gestosis*. Organization Gestosis-Press, 1975, pp. 297-301.
472. Sarles, M.E. et al.: Sodium excretion patterns during and following intravenous sodium chloride loads in normal and hypertensive pregnancies. *Am J Obstet Gynecol*, 102:1-7, 1968.
473. Schewitz, L.: Hypertension and renal disease in pregnancy. *Med Clin North Amer*, 55:47-69, 1971.
474. Schmeck, H.M., Jr.: Brain harm in US laid to food lack. *New York Times*, November 2, 1975.

475. Schoeller, D.A. et al.: Inaccuracies in self-reported intake identified by comparison with the doubly-labelled water method. *Can J Physiol Pharmacol*, 68:941-949, 1990.
476. Scholl, T.O. et al.: Use of multivitamin/mineral prenatal supplements: Influence on the outcome of pregnancy. *Am J Epidemiol*, 146:134-141, 1997.
477. Schulman, S.K. & Rosner, A.: A clinician's approach to initiating breastfeeding. In: Lifshitz, F: *Childhood nutrition*. Boca Raton, FL: CRC Press, 1995, pp. 21-31.
478. Schulz, D.M. et al.: Weights of organs of fetuses and infants. *Arch Pathol*, 74:244-250, 1962.
479. Schwartz, D.B., et al.: Gestational diabetes mellitus: metabolic and blood glucose parameters in singleton versus twin pregnancies. *Am J Obstet Gynecol*, 181:912-914, 1999.
480. Scott, J.R.: Current management of pre-eclampsia and eclampsia. *J Iowa Med Soc*, 66:209-211, 214-215, 1976.
481. Selenkow, H.A. et al.: Measurements and pathophysiologic significance of human placental lactogen. In: Pecile, A. & Fenzi, C.: *The foeto-placental unit*. Amsterdam: Excerpta Medica, 1969.
482. Semmelweis, I.P.: Die Aetiologie, der Begriff, und die Prophylaxis des Kindbettfiebers. Translated by Murphy, F.P.: The cause, concept, and prophylaxis of puerperal fever. *Medical Classics*, 5:339-773, 1941.
483. Shanklin, D.R.: The human placenta; a clinicopathologic study. *Obstet Gynecol*, 11:129-138, 1958.
484. Shanklin, D.R.: The pathology of prematurity. In: Cavanagh, D. & Talisman, M.R.: Prematurity and the obstetrician. New York: Appleton-Century-Crofts, 1969, pp. 189-194 (infarcts), pp. 458-459 (placental:fetal weight ratios), pp. 477-487 (hyaline membrane disease).
485. Shanklin, D.R.: The influence of placental lesions on the newborn infant. *Pediatr Clin North Amer*, 17:25-42, 1970.
486. Shanklin, D.R. & Cooke, R.J.: Effects of intrauterine growth on intestinal length in the human fetus. *Biol Neonat*, 64:76-81, 1993.
487. Shanklin, D.R. et al.: Nutrition and pregnancy: An invitational symposium: Part One. *J Reprod Med*, 7:199-219, 1971.
488. Shanklin, D.R. et al.: Nutrition and pregnancy: An invitational symposium: Part Two. *J Reprod Med*, 7:245-274, 1971.
489. Shanklin, D.R.: Making pregnancy healthy. *Medical Tribune*, New York, May 23, 1973.
490. Shanklin, D.R.: Of protein and pregnancy. *J Reprod Med*, 13:169, 1974.
491. Shanklin, D.R. & Sibai, B.M.: Ultrastructural aspects of pre-eclampsia. I. Placental bed and uterine boundary vessels. *Am J Obstet Gynecol*, 161:735-741, 1989.
492. Shanklin, D.R. & Sibai, B.M.: Ultrastructural aspects of pre-eclampsia. II. Mitochondrial changes. *Am J Obstet Gynecol*, 163:943-953, 1990.
493. Shanklin, D.R. et al.: The pathology of maternal mortality. *Am J Obstet Gynecol*, 165:1126-1155, 1991.

494. Shepherd, G.M.: *Neurobiology*, 2nd ed. New York: Oxford University Press, 1988, pp. 72-75.
495. Shneour, E.: *The malnourished mind*. New York: Doubleday, 1974.
496. Shoemaker, E.S. et al.: The effect of thiazide diuretics on placental function. *Tex Med*, 69:109-155, 1973.
497. Showstack, J.A. et al.: Factors associated with birthweight: an exploration of the roles of prenatal care and length of gestation. *Am J Public Health*, 74:1003-1008, 1984.
498. Silber, J.: Nutrition's role in learning. *New York Times*, November 16, 1975.
499. Simon, P. et al.: Absence of human chorionic somatomammotropin during pregnancy associated with two types of gene deletion. *Hum Genet*, 74:235-238, 1986.
500. Singer, J.E. et al.: Relationship of weight gain during pregnancy to birth weight and infant growth and development in the first year of life. *Obstet Gynecol*, 37:417-423, 1968.
501. Sivan, E. et al.: Leptin is present in human cord blood. *Diabetes*, 46:917-919, 1997.
502. Slot, H.M. et al.: Molybdenum-cofactor deficiency: an easily missed cause of neonatal convulsions. *Neuropediatrics*, 24:139-142, 1992.
503. Smith, C.A.: The effect of wartime starvation in Holland upon pregnancy and its product. *Am J Obstet Gynecol*, 53:599-608, 1947.
504. Snyder, D.K. et al.: Dietary carbohydrate content determines responsiveness to growth hormone in energy-restricted humans. *J Clin Endocrinol Metab*, 69:745-752, 1989.
505. Söder, G. et al.: Treatment of pre-eclampsia and eclampsia as a hypoperfusion syndrome. *Acta Anaesth Scand Suppl*, 57:71-78, 1975.
506. Somjen, G.: *Neurophysiology - the essentials*. Baltimore: Williams and Wilkins, 1983, pp. 438-439.
507. Sprinson, D.B. & Rittenberg, D.: The rate of utilization of ammonia for protein synthesis. *J Biol Chem*, 180:707-714, 1949.
508. Sprinson, D.B. & Rittenberg, D.: The rate of interaction of the amino acids of the diet with the tissue proteins. *J Biol Chem*, 180:715-726, 1949.
509. Stein, Z. et al.: Nutrition and mental performance. *Science*, 178:708-713, 1972.
510. Stein, Z. et al.: *Famine and human development: The Dutch hunger winter of 1944/45*. New York: Oxford University Press, 1975, p. 49.
511. Stern, W.C. et al.: Seizure susceptibility and brain amine levels following protein malnutrition during development in the rat. *Brain Research*, 79:375-384, 1974.
512. Stevenson, A.C., & Warnock, H.A.: Observations on the results of pregnancies in women resident in Belfast. *Ann Human Genet*, 23:382-420, 1958-59.
513. Stickle, G. & Ma, P.: Some social and medical correlates of pregnancy outcome. *Am J Obstet Gynec*, 127:162-166, 1977.
514. Stoch, M.B. & Smythe, P.M.: Does undernutrition during infancy inhibit brain growth and subsequent intellectual development? *Arch Dis Childh*,

- 38:546-552, 1963.
515. Strauss, M.B.: Observations on the etiology of the toxemias of pregnancy: The relationship of nutritional deficiency, hypoproteinemia, and elevated venous pressure to water retention in pregnancy. *Am J Med Sci*, 190:811-824, 1935.
516. Strong, S.J. & Corney, G.: *The placenta in twin pregnancy*. Oxford: Pergamon Press, 1967, p. 26.
517. Susser, E.S. & Lin, S.P.: Schizophrenia after prenatal exposure to the Dutch hunger winter of 1944-1945. *Arch Gen Psychiat*, 49:983-988, 1992.
518. Tanner, J.M. et al.: Standards from birth to maturity for height, weight, height velocity and weight velocity; British children 1965. (Part I) *Arch Dis Childh*, 41:454-471, 1966.
519. Tanner, J.M. et al.: Standards from birth to maturity for height, weight, height velocity and weight velocity; British children 1965. (Part II) *ibid*, 41:613-635, 1966.
520. Taylor, E.S.: Organic causes of minimal brain dysfunction. *Cont Med Digest*, August 1972, pp 822-823.
521. Taylor, J.L. & O'Leary, J.P.: Pregnancy following jejunoileal bypass: Effects on fetal outcome. *Obstet Gynecol*, 48:425-427, 1976.
522. Taylor, J.W. et al.: Thermal injury during pregnancy. *Obstet Gynecol*, 47:434-438, 1976.
523. Terris, M. & Glasser, M.: A life table analysis of the relation of prenatal care to prematurity. *Amer J Public Health*, 64:869-875, 1974.
524. Theobald, G.W.: Discussion on diet in pregnancy. *Proc R Soc Med*, 28:1388-1399, 1935.
525. Theuer, R.C.: Effect of oral contraceptive agents on vitamin and mineral needs. *J Reprod Med*, 8:13-19, 1972.
526. Thompson, T. & Reynolds J.: The results of intensive care therapy for neonates. I. Overall neonatal mortality rates. II. Neonatal mortality rates and long-term prognosis for low birth weight neonates. *J Perinat Med*, 5:59-75, 1977.
527. Thomson, A.M. & Hytten, F.E.: Body stores in human pregnancy and lactation. *Proc Nutr Soc*, 19:5-8, 1960.
528. Thomson, A.M. et al.: The energy cost of human lactation. *Br J Nutr*, 24:565-572, 1970.
529. Timmerman, M. et al.: Relationship of fetal alanine uptake and placental alanine metabolism to maternal alanine concentration. *Am J Physiol*, 275:E942-E950, 1998.
530. Timor-Tritsch, I. et al.: Classification of fetal movements. *Am J Obstet Gynec*, 126:70-77, 1976.
531. Titus, P. et al.: Fluctuations in blood sugar during eclampsia: Report of additional cases. *Am J Obstet Gynecol*, 19:16-25, 1930.
532. Tobin, A.: Organic causes of minimal brain dysfunction. Perinatal origin in minimal cerebral lesions. *JAMA*, 277:1207-1214, 1971.
533. Tompkins, W.T.: The significance of nutritional deficiency in pregnancy: A preliminary report. *J Int Coll Surg*, 4:147-154, 1941.
534. Tompkins, W. & Wiehl, D.T.: Nutritional deficiencies as a causal factor in

- toxemia and premature labor. *Am J Obstet Gynecol*, 62:898-919, 1951.
535. Tompkins, W. & Wiehl, D.: Nutrition and nutritional deficiencies as related to the premature. *Pediatr Clin North Amer*, 1:687-708, 1954.
536. Toverud, G.: The influence of nutrition on the course of pregnancy. *Milbank Mem Fund Q*, 28:482-485, 1950.
537. Toyoda, N., et al.: Insulin binding, glucose oxidation and methylglucose transport in isolated adipocytes from pregnant rats near term. *Endocrinology*, 116:998-1002, 1985.
538. Toyoda, N., et al.: Postbinding insulin resistance around parturition in the isolated rat epitrochlearis muscle. *Am J Obstet Gynec*, 165:1475-1480, 1991.
539. Tresadern, J.C. et al.: Successful completed pregnancy in a patient maintained on home parenteral nutrition. *Br Med J*, 286:602-603, 1983.
540. Tronick, E.Z. & Beeghly, M.: Prenatal cocaine exposure, child development, and the compromising effects of cumulative risk. *Clin Perinatol*, 26:151-171, 1999.
541. Trucco, J.T., Brown A.K.: Neonatal manifestations of hereditary spherocytosis. *Am J Dis Child*, 113:263-270, 1967.
542. Tsai, M. et al.: Shaped by life in the womb. *Newsweek*, 134:50-57, (September 27), 1999.
543. Valman, H.B.: Intelligence after malnutrition caused by neonatal resection of ileum. *Lancet*, 1:425-427, 1974.
544. vanVeen, L.C.P. et al.: Leucine disposal and oxidation rates in the fetal lamb. *Metabolism*, 36:48-53, 1987.
545. Venkatachalam, P.S.: Maternal nutritional status and its effect on the newborn. *Bull WHO*, 26:193-201, 1962.
546. Viscarello, R.R. et al.: Limb-body wall complex associated with cocaine abuse: Further evidence of cocaine's teratogenicity. *Obstet Gynecol*, 80:523-526, 1992.
547. Viteri, F.E.: The consequences of iron deficiency and anemia in pregnancy. In: Allen, L. et al.: *Nutrient regulation during pregnancy, lactation, and infant growth*. New York: Plenum, 1994, pp 127-139.
548. von Wendt, L. et al.: Prenatal brain damage in nonketotic hyperglycinemia. *Am J Dis Child*, 135:1072, 1981 (letter).
549. Waber, D.P. et al.: Nutritional supplementation, maternal education, and cognitive development of infants at risk of malnutrition. *Am J Clin Nutr*, 34:807-813, 1981.
550. Waldrop, M.M.: *Complexity; the emerging science at the edge of order and chaos*. New York: Simon & Schuster, 1982, 380 p.
551. Wang, Y. & Walsh, S.W.: TNF alpha concentrations and mRNA expression are increased in pre-eclamptic placentas. *J Reprod Immunol*, 32:157-169, 1996.
552. Warkany, J. et al.: Intrauterine growth retardation. *Am J Dis Child*, 102:127-157, 1961.
553. Warner, E.A. et al.: Diabetic ketoacidosis associated with cocaine use. *Arch Intern Med*, 158:1799-1802, 1998.
554. Waterlow, J.C.: Observations on the mechanism of adaptation to low protein intakes. *Lancet*, 2:1091-1097, 1968.

555. Weingold, A.: Intrauterine growth retardation: Obstetrical aspects. *J Reprod Med*, 14:244-247, 1975.
556. Weseley, A.C. & Douglas G.W.: Continuous use of chlorothiazide for prevention of toxemia of pregnancy. *Obstet Gynecol*, 19:355-358, 1962.
557. West, C.D. & Kemper, T.L.: The effect of a low protein diet on the anatomical development of the rat brain. *Brain Research*, 107:221-237, 1976.
558. Widdowson, E.M.: Nutrition and lactation. In: Winick, M.: *Nutritional disorders of American women*. New York: John Wiley & Sons, 1977, pp. 67-75.
559. Wiener, G. et al.: Correlates of low birth weight: Psychological status at eight to ten years of age. *Pediatr Res*, 2:110-118, 1968.
560. Wiener, G. & Milton, T.: Demographic correlates of low birth weight. *Am J Epidemiol*, 91:260-272, 1970.
561. Williams, C. et al.: Protein, amino acid, and caloric intakes of selected pregnant women. *J Am Diet Assoc*, 78:28-35, 1981.
562. Williams, C.D.: Malnutrition. *Lancet*, 2:342-344, 1962
563. Williams, R.L. & Chen, P.M.: Identifying the sources of the recent decline in perinatal mortality rates in California. *N Engl J Med*, 306:207-214, 1982.
564. Williams, R.: Intrauterine growth curves: Intra- and international comparisons with different ethnic groups in California. *Prev Med*, 4:163-172, 1975.
565. Winick, M.: Changes in nucleic acid and protein content of the human brain during growth. *Pediatr Res*, 2:352-355, 1968.
566. Winick, M. (Ed.): *Nutrition and development*. New York: Wiley-Interscience, 1972, p 72.
567. Winick, M.: *Hunger disease: Studies by the Jewish physicians in the Warsaw ghetto*. New York: John Wiley & Sons, 1979, 261 p.
568. Winick, M. et al.: Cellular growth in human placenta. I. Normal placental growth. *Pediatr*, 39:248-251, 1967.
569. Winick, M. & Rosso, P.: The effect of severe early malnutrition on cellular growth of human brain. *Pediatr Res*, 3:181-184, 1969.
570. Wise, P.H. et al.: Infant mortality increase despite high access to tertiary care: an evolving relationship among infant mortality, health care, and socio-economic change. *Pediatrics*, 81:542-548, 1988.
571. Wolff, J.A. et al.: Alanine decreases the protein requirements of infants with inborn errors of amino acid metabolism. *J Neurogenet*, 2:41-49, 1985.
572. Wu, G. et al.: Maternal dietary protein deficiency decreases amino acid concentrations in fetal plasma and allantoic fluid of pigs. *J Nutr*, 128:894-902, 1998.
573. Wu, H. & Wu, D.Y.: Influence of feeding schedule on nitrogen utilization and excretion. *Proc Soc Exp Biol Med*, 74:78-82, 1950.
574. Wynn, M. & Wynn, A.: *The protection of maternity and infancy*. London: EH Baker & Co, 1974.
575. Wynn, M & Wynn, A: *Nutrition counselling in the prevention of low birth-weight*. London: Foundation for Education and Research in Child-Bearing, 1975.
576. Yerushalmy, J. et al.: Studies in childbirth mortality. III. Puerperal fatality in relation to mother's previous infant loss. *Public Health Rep*, 56:1463-1481, 1941.

577. Young, M. & Widdowson, E.M.: The influence of diets deficient in energy, or in protein, on conceptus weight, and the placental transfer of a non-metabolisable amino acid in the guinea pig. *Biol Neonate*, 27:184-191, 1975.
578. Zhang, Y. et al.: Positional cloning of the mouse obese gene and its human homologue. *Nature*, 372:425-432, 1994 (errata, ibid 374:479, 1995).
579. Zitrin, A. et al.: Pre- and paranatal factors in mental disorders of children. *J Nerv Ment Dis*, 139:357-361, 1964.
580. Zmora E. et al.: Multiple nutritional deficiencies in infants from a strict vegetarian community. *Am J Dis Child*, 133:141-144, 1979.
581. Advantages of supplementary alanine in infants with genetic defects of amino acid metabolism. *Nutr Rev*, 44:164-166, 1986.
582. Albumin concentrate can be used for mild pre-eclampsia. *Obstet Gynecol News*, October 1, 1974.
583. *A study of infant mortality from linked records: Comparison of neonatal mortality from two cohort studies*. Washington, DC, US Department of Health, Education, and Welfare, 1972.
584. *Certain thiazides: Their use in pregnancy*. Obstetrics and Gynecology Advisory Committee, Food and Drug Administration, July 17, 1975, pp 1-98.
585. Department of Health: *Dietary reference values for food energy and nutrients for the United Kingdom*. London: Her Majesty's Stationery Office, 1991.
586. Food Consumption of Urban Families in the US. US Department of Agriculture Information Bulletin, No. 132, Washington, DC: US Government Printing Office, October 1954.
587. Health, United States, 1998; HIV/AIDS Surveillance Report, Vol. 9, No. 2, National Center for Health Statistics, U.S. Department of Health and Human Services.
588. *Hunger: USA*. Citizen's Board of Inquiry, Boston, Beacon Press, 1968.
589. Invisible deficiency endangers unborn. *Tech Rev*, December 1974, pp 63-64.
590. Judges 13:14.
591. Monitoring the Future, University of Michigan Institute for Social Research; National Institute on Drug Abuse, 1998.
592. *Nutritional supplementation and the outcome of pregnancy*. Washington, DC, National Academy of Sciences, 1973.
593. Observation on maternity care and pediatric care in the People's Republic. In: Report of the Medical Delegation to the People's Republic of China. Washington, DC, National Academy of Sciences, 1973.
594. *Prevention handbook*. National Association for Retarded Citizens, 1974.
595. *Recommended daily allowances*, 8th ed. Food and Nutrition Board, National Research Council, Washington. D.C., National Academy of Sciences, 1974.
596. Substance Abuse and Mental Health Services Administration, U.S. Dept. of Health and Human Services, 1997.
597. *Taber's cyclopedic medical dictionary*, 12th ed., Thomas, C (Ed.), Philadelphia: FA Davis Co., 1973.
598. *The demographic yearbook*. UN Department of Economic and Social Affairs, 1974.
599. The great eclampsia mystery, or the case of the empty plaque. *Med World News*,

- July 20, 1973, pp 41-52.
600. Toxaemia: A disease of prejudice? *World Med J*, 21:70-72, 1974.
601. *US vital statistics: Natality*. Rockville, MD: National Center for Health Statistics, 1974.
602. _____: Rockville, MD: National Center for Health Statistics, 1950.
603. *White House Conference on Food, Nutrition, and Health*. Washington, DC: US Government Printing Office, 1970.
604. *World almanac*, 1999: p. 873 (births in the United States, 1990-1997).
605. *World almanac*, 1999: p. 875 (infant mortality in the United States, 1997).
606. Infant mortality – United States, 1990. *MMWR*, 42:161-165, 1993.
607. Fetal alcohol syndrome – United States, 1979-1992. *MMWR*, 42:339-341, 1993.
608. Zidovudine for the prevention of HIV transmission from other to infant. *MMWR*, 43:285-287, 1994.
609. Increasing incidence of low birthweight – United States, 1981-1991. *MMWR*, 43:335-339, 1994.
610. Birth outcomes following zidovudine therapy in pregnant women. *MMWR*, 43:409, 415-416, 1994.
611. Down syndrome prevalence at birth – United States, 1983-1990. *MMWR*, 43:617-622, 1994.
612. Infant mortality – United States, 1992. *MMWR*, 43:905-909, 1994.
613. Economic costs of birth defects and cerebral palsy – United States, 1992. *MMWR*, 44:694-699, 1995.
614. Poverty and infant mortality – United States, 1992. *MMWR*, 44:922-927, 1995.
615. Nutritional status of children participating in the special supplemental nutrition program for Women, Infants, and Children – United States, 1988-1991. *MMWR*, 45:65-69, 1996.
616. Infant mortality – United States, 1993. *MMWR*, 45:211-215, 1996.
617. Spontaneous abortions possibly related to ingestion of nitrate-contaminated well water – LaGrange County, Indiana, 1991-1994. *MMWR*, 45:569-572, 1996.
618. Abortion surveillance – United States, 1992. *MMWR*, 45:SS-3, 1996.
619. Use of folic acid-containing supplements among women of childbearing age – United States, 1997. *MMWR*, 47:131-134, 1998.
620. Healthier mothers and babies. *MMWR*, 48:849-850, 852-857, 1999.
621. Prevalence of selected maternal and infant characteristics, pregnancy risk assessment monitoring system (PRAMS), 1997. *MMWR*, 48:SS-5:1-37, 1999.

INDEX

A

- Abdominal circumference, fetal, 105
Abdominal delivery
in Motherwell Protocol, 64–66
need for, by diet, 192, 194
Aberdeen University review of Motherwell Protocol, 66–70
Abrams, B. and Parker, J.D., 215, 224
Abruptio placenta, 59, 188, 195
and cerebral palsy, 165
and food intake, 56
and mental deficit, 178, 188
and poor nutrition, 118, 129
and reading disorders, 185
in salt restriction, 87
Absorptive capacity of newborns, 218
Acardiac twin, 127
Accelerated starvation, 20, 110
Acetoacetate, 19, 20
Acetylcholine, 221
Acidosis, 141
Acquired immunodeficiency syndrome (AIDS), 9
Adaptation to intake, smallness as, 19
Adaptive capacity, 182
Adenocarcinoma of pancreas, 46
Adipocytes, 107
Adolescence, effects of malnutrition, 214
Adrenal changes, 84, 93
African-Americans, 207
Alanine, 3, 105, 106, 111
Alberman, E., 190
Albumin, serum, 32, 38, 100, 101
and birth weight, 81
and perinatal mortality, 100
and salt therapy, 100

- synthesis by liver, 102
Alcohol, 10, 148
Aldosterone in pregnancy, 83, 84, 111
exhaustion of system, 93
injection in pregnant rats, 93
Alleviation of toxemia, temporary, 96
 α -aminobutyrate, 19
 α -ketoisocaproic acid, 105
Amenorrhea in malnutrition, 4, 14, 22
Amino acids
aliquot feeding, 235–237
branched chain, 3
catabolism, 20
effect of dietary restriction, 106
essential, 111, 235
lack of, 50
intragastric synthesis, 69
limit on absorptive capacity, 69
neutral, uptake, 105
plasma free, low birth weight infants, 220
pool, lack of, 19, 69, 237
predelivery infusion, 235
rare disorders, 3, 240
resynthesis in placenta, 105, 152
simultaneous necessity, 234–236
timing of repletion, 234–236
transplacental metabolism, 105
transporter proteins, 105–107
Aminoaciduria, from use of infant formulas, 220
Ammonemia, from use of infant formulas, 220
Amniotic fluid, 19
Amphetamine, 10
Amyl nitrite, 10
Anabolic nature of pregnancy, 21

- Analytic methods in WIC, 145
 Andrews, B.F., viii, 239
 Anemia, masked by hypovolemia, 92
 maternal, pregnancy complications, 193
 neonatal or infantile, 41
 Anencephaly, 3
 Angiotensin I, 84
 Angiotensin II, 84
 in gestosis (preeclamptic toxemia), 84
 Animal studies, 24, 232, 234, 235
 carcass analysis, 231
 experimental diabetes, 234
 food cycle studies, 234–236
 leptin deficient mice, 203
 protein deficiency and repletion, 234
 Anomalies
 in births during starvation, 15
 long term results, 141
 and low birth weight, 141
 Anoxia as etymological fog, 240
 Anoxia as proxy for uncertain
 pathogenesis, 76, 77
 Antibody:insulin complexes, 107
 Antiinsulin effects of placental lactogen, 218
 Antioxidant compartment, 233, 234
 Antipoverty programs, for prevention
 of malnutrition, 167
 Antonov, A.N., 13
 Aphagia, 221
 Apnea
 Early and development, 140
 Late and development, 140, 195
 Apoptosis, 96
 Appetite changes, hypothesis, 51
 Applied scientific nutrition, 113
 Architecture, brain, 75
 after low protein diet, 26
 Arginine, 106
 Army (U.S.) food transfer, 18
 Arterial oxygen saturation, 118
 Asphyxia, neonatal, 159, 172, 187
 Assessment, nutritional studies, 114
 postnatal, 179
 reliability, neurological function, 125,
 138, 189
 superficial, 176
 ultrasophisticated, 22
 Assumptions behind WIC, 144
 Astin, M., 229
 Asymmetric categories in data, 116
 Attention span, 76, 167
 Augmentation of labor by oxytocin, 64
 Australian studies, 113, 114
 Autism, 168
 Autopsies, malnourished infants, 115–117
 Axon size, 75
 Azotemia, from use of formulas, 220
- B**
- Babson, S.G., 125, 126
 Bacola, E., 140, 194, 195
 Bacteriuria, 90
 Bainbridge, R. and Tsang, R., 218
 Bakketeg, L.S., 229
 Baldwin, V.J., 160, 161
 Balfour, M.I., 114, 115
 Baltimore studies, 171, 178, 196
 Barbiturates, 100
 Basal metabolic rate, 157
 Basket cells, cerebellum, 25
 Battaglia, F.C., 104, 105, 119, 128
 Bayley Scales of Development, 189
 Behavioral disorders, 115, 128, 129, 134,
 166, 181
 Behavioral stability and birth weight, 167
 Bellshill Hospital, 183, 204, 205
 Benefit, noncompliance, restrictive diets, 98
 Benton, A.L., 166
 Berger, G., 175, 176
 Beriberi, 95
 β-carotene, 234
 β-hydroxybutyrate, 19
 Biblical reference, 3
 Bilirubin, elevated, 8, 76
 Biochemists, 18
 Biological basis for fetal weight gain, 21, 200
 Biological foundation of pregnancy, 156,
 240
 Biological imperative, 205, 206, 223–242
 early fulfillment, 242
 Biological limit on birth weight, 201
 Biological limits, xii, 131, 132, 200, 224
 Biological meaning, 59, 132, 146, 160
 Biological range of birth weight, 21, 200,
 215
 Birch, H. and Gussow, J., 210, 214
 Birth certificates
 reported complications, 164
 socioeconomic status, 133–137
 Birth complications and cerebral palsy,

- 159, 161–166
Birth length, 27
at high altitude, 118
in twins, 126
Birth length measurement, 108
Birth trauma, 192
Birth weight, 124–158
and albumin level, 81
and cerebral palsy, 161
and developmental status, 124, 126, 127,
129, 130, 132, 134, 135, 137, 139
at high altitude, 117
and infant mortality, 128
and I.Q., 7, 126, 127, 129–134
and length of gestation, 203
and length of time, prenatal program, 34
and maternal nutrition, 46, 48–53,
124–158
as marker for infant health, 6, 15, 28,
128, 136, 197
and mental deficiency, 129, 168, 170, 172
in Motherwell Protocol, 182, 183
and neuropsychiatric disorders, 124, 128,
165, 167, 168
and nutritional influence, 28
in preeclampsia, 72
in primigravidae, 142, 143
relative to prior pregnancy outcome,
150, 229, 230
and supplementation, 45
at term, 200
and total body protein turnover, 220
in twins, 125, 130–133
Birth weight limit, 201
Birth weight measurement, 108
Birth weight ratio, 21
Black, A.E. and Goldberg, G.R., 238
Blacks, low additive effect in complications,
171
Bland, R., 101–103
Blastocyst formation, 224
Blindness, 128
Blood glucose, immediate postnatal, 109
maternal, 109, 110
Blood pressure control, 77
and hemoglobin values, 61
Blood transfusion, 60, 92
Blood urea nitrogen (BUN), 92
Blood volume expansion in pregnancy
48, 84
Blood volume, fetal, in diabetic pregnancy,
111, 112
Boehm, F., 175
Bourne, A.W., 228
Bower, D., 93
Brain cell deficit, 74
Brain cell division, 71
Brain complexity, 71
Brain damage, irreversible, 71
Brain development, 71
and malnutrition, 71–76
rapidity of, 71, 75
Brain DNA, 74
Brain function and food intake, 221
Brain growth phases, 25, 75
Brain protein, 72, 73
Brain RNA, 72, 74
Brain underdevelopment, 71–76
Brain weight, 26, 71–73, 147
Breast feeding and prenatal diet, 41, 215–217
Breast milk (see also human milk), 22,
215–218
banked, 216
protein content, 216, 217, 229
quality, 215–217
variation in content, 216, 217
volume, 22, 217
Brewer, T.H., ix, 52, 53, 94, 95, 97
Briend, A., 158
Britain
comparative studies, 115, 225–227
government food supplements, 15
mean daily diet, comparative, 67
prematurity studies, 225–227
World War II, 115
British Medical Research Council, 213
Bronchitis, 41
Bronzino, J.D., 26
Brown, M.C., 66–69
Buescher, P.A., 152
Burke, B.S., 27, 29, 30, 192
Butyl nitrite, 10
Bypass, intestinal, and birth weight, 31–33

C

- Calcium intake, 45, 47, 99, 114
in WIC, 146
California studies, 207, 208
Caloric costs of fetal protein synthesis, 237
Caloric cost of pregnancy, cumulative, 231

- Caloric deficiency or deprivation, 19, 20, 47, 197
Calorie homeostasis, 107
Caloric intake, Aberdeen, 69
as limiting factor, 49–51
Motherwell, 69
Caloric replenishment, 221
Caloric reserves in obesity, 45
Caloric restriction, 206
in obesity, 21
Caloric supplementation, 78
ad libitum, 98
and excessive maternal weight gain, 198
and low birth weight, 36, 44
and placental weight, 77–79
raising birth weight, 49
Caloric threshold, 49, 78, 153
Cameron, C.S. and Graham, S., 44, 53
Canadian Council on Nutrition, 34
Canadian poverty level, 33
studies, 33–37
Cancer, 46, 76
Cannon, P.R., 235, 236
Cape Town, South Africa, 212
Carbohydrate intolerance, 104
Carbohydrate surplus, 107
Carbonic anhydrase, 117
Carbon monoxide, 117
Cardiac disease, advanced, 42
Cardiovascular disorders, 76
Casein in diet, 25
Catalase, 234
Causation, social, and intelligence, 17
Cause of death, low birth weight (in U.S.), 6
Cell biology, 225
Cell cycle time, 25
Cell organelles, 96
Cell proliferation, brain, and malnutrition, 25–26, 71–75
Cell signalling, redundancy, 225
Cellular effects per dietary class, 117
Cellular sites and free radicals, 233, 234
Centers for Disease Control (C.D.C.), 176, 184
Central nervous system, complexity, 71, 75
Cephalization, 72
Cerebellum, differentiation, 75
effect of low protein diet, 25
Cerebral palsy, 17, 128–129, 135, 165, 190
and birth order, 163
and birth weight, 159, 161–164, 179–182
in the continuum of reproductive casualty, 165, 166
contributory injury, 162
and fetal distress, 178
independent causes, 161
interdependent factors, 161
mild, confounding effect, 159
and multiple births, 160
in Norway, 165
and obstetrical operations, 164, 169
and paranatal complications, 159, 161–163
and perinatal mortality, 159
prevalence, 190
and singleton births, 159, 179
and stillbirth, 165
Cerebrum, 75
Cetin, I., 106
Chemokine(s) as pregnancy “toxin,” 96
Chesley, L. C., 91, 94, 223, 224, 228
Chilean studies, 72–74
China, Peoples Republic, premature birth, 6
Choline, 55
Chorionic somatomammotropin, 218
Chromosomal abnormalities, 167
Chronome, 238
Churchill, J., 138, 139
Cigaretts, 10, 117, 148
Circadian rhythms, 234, 238
Circumference of head, newborn, 34, 71, 212
at high altitude, 118
in preeclampsia, 72
Cities excluded from WIC, 145
Citric acid cycle, 18
Citrulline, 106
Clinical brain damage, absence, Norwegian program, 42
Clomiphene induced ovulation, 160
Cocaine, 9, 10, 113
teratological effect, 209
Cognitive potential, and malnutrition, 76, 180, 181
Cohn, C., 234
Collaborative Study of N.I.H., 7, 8, 79, 114, 188, 197
deficiencies, 7, 188, 191
high birth weight, 191
mortality rates, 114, 146
neurological state of newborns, 192

- omissions, 161
placental weights, 79
placenta previa, 189
redefined methodology, 188
and weight gain, 202
Colloid osmotic pressure, plasma, 85, 102, 199
without antepartum hemorrhage, 102
Colorado,
Down syndrome, 184
high altitude, 118, 119
Common etiology for maternal and fetal disorders, 161
Comparative anatomy, human brain, by age, 71, 72
Comparison basis using expectation data, 116
Compartments
interstitial extravascular, 83
intravascular, 83
metabolic, 233
in pregnancy, 231, 232
pregnancy hormones, 232
proteins, 86
skeletal muscle versus liver, for protein, 231
Complexity theory, 10
Complex partial seizures, maternal, 169
Complex processes, 224
Complications of pregnancy, 164
and cerebral palsy, 166, 168, 180
and low birth weight, 182, 190
and malnutrition, 193
Confounding factors in ethnic:racial diversity, 207
excluding early perinatal deaths in WIC, 148
excluding low birth weight cases from analysis, 196
in gestational homeostasis, 225
neonatal care, 104, 119, 128, 132, 147
prior good nutrition, 55
salt and weight control, 43, 82, 86, 87
social causation, 17
Congenital anomalies, 141
Congenital defects, central nervous system, 17
Congenital heart disease, 141
Congenital spherocytosis, 76
Connectivity, neural, 71, 75
Conservation of energy, 157
Continuum of nutritional problems, 220
Continuum of reproductive casualty, 166–170, 174–175, 197
Contraindications to surgical induction, 63–64
Contrainsulin hormones, 107
Convulsions, neonatal, 169, 171, 172, 187
Cooper, D.W., 228
Cord blood, protein level
and birth weight, 102
and length of gestation, 102, 103
and mortality, 101–103
and respiratory distress syndrome, 101–103
Corn based cereal, 50, 78
Cost of food supplementation, 36, 39
Course of pregnancy, factors, 169
Crack cocaine, 10
Cravioto, J., and Robles, B., 214
Creatinine clearance, 100
Crede's maneuver, 62
Critical periods of brain growth, 123
Critique of analytic studies
Collaborative Study, 78, 188–189
Davies and Evans, 220–221
Finnerty, 88–91
Stein-Susser, 16–17
Vanderbilt Co-operative, 55–57
WIC, 144–154
Crohn disease, 32
Cultural conditioning, 234, 237
Cultural-social-habitual-economic model, 18
Cumulative
calories in pregnancy, 232
effects of substances, 111, 218
protein in pregnancy, 231
Cuzco, Peru, 117
Cyanosis, neonatal, 172, 187
Cysteine, 237
Cystine, 106, 237
Cytochemistry, 225
Cytokines, 82, 96, 225
Cytoplasm, reduction in, 116

D

- Dangerous drugs, 5
Darby, W.J., 55
Darby appetite hypothesis, 51
Dark room treatment of preeclampsia, 96

- Data accretion, critique of pessimistic view, 156
- Data analysis, 10
- Data failure, 90
- Data recalculation, 224
- Davies, D.P. and Evans, T.J., 220
- Day of atonement, 20
- Deafness in low birth weight, 8
- Deaths, postneonatal, 6
- Decline in births, due to starvation, 12, 14
- Deficiency, single nutrient, 47, 82
- Deficiency states
- borderline and child health, 55
 - and eclampsia, 96
 - essential ingredients, 3
 - salt and pregnancy outcome, 194
 - singular and placental lesions, 82
- Dehydroisoandrosterone sulfate (DHAS), 92
- Delgado, H.L., 22
- Demographic correlates and low birth weight, 197, 206
- Demographic factors, 240
- Dendrites and synapses, 26, 75
- Dentate gyrus, 26
- Dentate nucleus, 26
- Denver, altitude and neonatal death rate, 118, 119, 128
- Dermal burns, 209
- Developmental disability, 14
- Development and malnutrition, 132
- Developmental Quotients (Gesell), 115, 125, 214
- and birth weight, 141
 - timing of malnutrition, 214
 - and toxemia, 115
- Developmental status of brain, 71
- Developmental time tables, brain, 25
- Diabetes mellitus, 104, 107
- gestational, 19
 - juvenile, "round the clock" control, 234
 - ketacidosis after cocaine, 113, 209
 - latent, 201
- Dieckmann, W.J., 30, 184, 216, 223, 224, 237
- Diet, prenatal, and birth weight, 28, 29, 204–206
- Dietary deficiency and toxemia, 94, 195
- Dietary intake, 15
- Dietary histories, 38, 199, 238
- bias toward underreporting, 238
 - during wartime, 53
- Dietary intervention and I.Q., 214
- Dietary motivation, 144
- Dietary protein
- as energy source, 38
 - from teff, protective against toxemia, 114
- Dietary rating, 47, 48
- Dietary restrictions, 82, 94, 194
- Dietary sources of sodium, 95
- Diet index, 59
- Differential growth, human brain, 75
- Diplegia, spastic, 128
- Disabilities, developmental, and malnutrition, 3, 4, 24
- Discontinuity between maternal weight gain and birth weight, 43, 132, 197, 200, 201, 241
- District of Columbia, 36, 88–92
- Diuretic use in pregnancy, 36, 88–92
- double blind studies, 88, 91
 - maternal death, 91
 - medical complications, 91
- Dizygotic twins, 160
- DNA, human brain, 74
- Dodge, E. and Frost, T., 98, 99
- Donnet, M.L. and Stanfield, J.P., 219
- Double blind study, 30
- Douglas, B.H., 94
- Douglas, J.W.B., 225–227
- Down syndrome, 70, 183–184
- Drew-Smythe catheter, 63
- Drillien, C.M., 128–130, 132–134, 142, 190, 195
- Drugs, dangerous, 5
- Duke Hospital, 96, 192
- Duration of pregnancy and neonatal weight, 203
- Durham, North Carolina, 96, 192
- Dutch studies, 14–18, 127
- Dysmaturity, 141
- Dystocia
- and cerebral palsy, 169, 188
 - and diet, 193
 - shoulder dystocia, 191

E

- Eastman, N.J., 165
- Ebbs, J.H., 38, 193
- Eclampsia
- (see also gestosis, preeclampsia, toxemia), 59, 96, 113–114

- and fluctuant blood glucose, 104
and hyponatremia, 92
and serum osmotic pressure, 85
Economic status and I.Q., 133-137
correlated with birth weight, 136, 137
Edema of pregnancy
pathological, 85
physiological, 85
Educational advancement and birth weight, 136, 137
Educational difficulties, 129, 210
Educational nutrition projects
on food for pregnancy in obesity, 199
nonsupplementative, 52-53
supplementative, 58-70
Education, level of, 134
Efficiency, comparative metabolic, xii
Electroencephalograph (EEG), abnormal, 128
Electrolyte imbalance, 91
Electroneural information, 75
Emotional difficulties, 128
Encymonic atelositesis, 95
Endocrine profiles in pregnancy, 218
Endothelial dysfunction in gestosis, 96, 229
Energy costs, xii, 32, 45, 78, 157, 199
extra obligatory, 21
Energy intake, 14, 152-157, 199
Energy physiology, 234
measurement versus dietary records, 238
per diem, 157, 234-238
pregnancy totals, 157, 231, 241
England, low birth weight, World War I, 15
Engleson, G., 141
Environmental influences on fetal development, 28-28, 44, 136, 169
Enzymatic changes in gestosis, 96
Enzymatic detoxification, 97
Epidemiologic investigation, xii
Epigenetic factors in mental defect, 139, 166-168, 170, 171
Epilepsy, event precedent, 76
genetic causes, 169
and low birth weight, 168, 169
states, 172
subclinical, 167
Epileptogenic stimuli, 26
Essential hypertension, 143
Essential nutrients, 197
iron, 47, 149
sodium, 86
Estradiol, 92
Estrogen excretion, urinary
following diuretics, 92
following IV albumin, 100
in hyperinsulinism, 104
in malnutrition, 81
Ethics of deprivation studies, 24
Ethiopian studies, 114
Etymological fog, 240
Euglycemic fetal macrosomia, 107
Evaluation, difficulties in, 114
Excess body water without edema, 85-86
Exclusions from study data, 49, 138, 172, 196, 204
Exhaustion of aldosterone secretion, 93
Expansion of plasma volume, 147
Expectations on size of newborn, 151
Expertise, clinical level, 175, 176
- F**
- Facilitated metabolism, 20
Failed induction of labor, 65, 66, 144
Family income and pregnancy outcome, 33, 47, 48, 78
Farmer, A.P., 18
Fasting, effects of, 19, 20, 111
Fat depots in malnourishment recovery, 221
Fat mobilization, 111
FDA hearing on diuretics, 91
FDA procedure, ideal assessment, commentary, 19
Fee, B.A. and Weil, W.B., 110
Felig, P., 19
Ferguson, J.H., 56
Ferritin, 149
Fertilization, 224
Fetal activity and perinatal mortality, 110
Fetal adrenal weight, 117
Fetal alcohol syndrome, 10
Fetal distress, 178
and hypovolemia, 97
Fetal growth pattern and late life glucose intolerance, 113
Fetal growth retardation, 80, 81, 127
in underweight mothers, 110
Fetal liver
glycine metabolism, 104
weight, 117
Fetal macrosomia, 107-109

- Finland, disability:mortality ratio, 4
 Finnerty, F.A., Jr., 88-90, 227
 First marriage age, 10
 First order plausibility, 189
 Folic acid, 3, 22
 Food, xii
 Food and Drug Administration, hearing,
 diuretics in pregnancy, 91
 Food and Nutrition Service, U.S.D.A., 144
 Food deprivation, 17
 Food intake, 120
 and brain function, 221
 diaries, 157
 home environment, 68
 hospital environment, 68
 optimal, 18
 outpatient environment, 68, 69
 packaging, 18
 reduced, effect in pregnancy, 110-111
 as small, frequent portions, 238
 Franco-Prussian War, 215
 Free fatty acids, 19, 20
 Freinkel, N., 110
 Freud, S., 159
 Friedman, E.A., 89
 Full optimism hypothesis, 175
 Functional effects in brain, prenatal
 deprivation, irreversible, 26
 Functional maturation, 182
 Fused twins, 127
 Future programs, 242
- G**
- Gambian studies, 151, 154-158
 γ -aminobutyric acid, 221
 Gaull, G.E., 220
 General Accounting Office, 189
 Genetic matrix, 3, 167
 Genetically transmitted metabolic disorders,
 3, 167
 Genetic process, Down syndrome, 184
 Geographic studies
 Alabama, 99
 Australia, 113-114
 Baltimore, 171, 179, 196
 Britain, 15, 225-227
 California, 207, 208
 Canada, 33-38
 Denver, Colorado, 118, 119, 128
 East Africa, 18
 England, 15, 16
 Ethiopia, 114
 Gambia, 151, 154-158
 Germany, 15, 16
 Glasgow, 44, 53-54, 219
 Guatemala, 48-52, 77, 79
 Holland, 14-18, 127
 India, 93, 215
 Indonesia, 213
 Jamaica, 213
 Japan, 17, 18
 Lake County, Colorado, 118, 119
 Leningrad, 12-14, 18
 Los Angeles, 118
 Maryland, 179
 Mexico, 52, 118
 Montreal, 33-38
 Motherwell, 58-70, 182-184, 204-206
 Nashville, 56
 New York State, 159-164
 North Carolina, 95-96, 152, 175, 192
 Norway, 41, 165, 229-230
 Ohio, 121-123
 Paris, 215
 Philippines, 30, 31
 Poland, 17
 Russia, 12-14
 Scotland, 46, 53, 54, 58-70, 142-144,
 182, 183, 204-206, 219
 Senegal, 157-158
 South Africa, 212
 Taiwan, 52
 Tennessee, 56
 Toronto, 38
 Wales, 228
 Germany, birth weights, World War I, 15
 Gesell Developmental Quotient, 124, 214
 Gestation
 as biological function, 225
 at high altitude, 118
 length of, and birth weight, 45, 128, 141,
 203
 and growth of uterus, 9, 190-191
 and nutritional supplements, 45
 Gestational diabetes mellitus, 19
 and maturity onset diabetes, 112
 Gestational dysnutrition, 72, 75
 Gestational third factor, undetermined, 132
 Gestational hormonal changes, 83
 Gestational index, 59, 92

- Gestational profile, 143, 201
Gestational time, animals and humans, 25
Gestosis
(see also eclampsia, preeclampsia, toxemia), 59, 94–100, 192
albumin, 99
animal models, 94
antigestotic state, 240
and cytokines, 82
and dietary success, 87, 194
E-gestosis, 87, 143, 144
etiology, 94–97, 99
and globulins, 99
and high salt diet, 88, 94
history of syndrome and treatment, 96
and hyperinsulinemia, 104
irrational theories and treatments, 94
lack of renal factor in causation, 95
and neonatal deaths, 114
possible paternal factor, 229
and pregnancy complications, 188
primigravidae, elderly, 143
and renin-angiotension-aldosterone system, 86
and stillbirth, 114
thyroid function, 229
water turnover, 232
when woman is product of gestotic pregnancy, 228
Gilford's progeria, 17
Glasgow area communities, 206
Glasgow study of 1944, 44
Glia, formation, 75
Glomerular filtration rate, 83, 92
Glomerular lesions, 92, 188
Glossitis, 42
Gluconeogenesis, 20, 107, 111, 218
hepatic, 21
rate limiting enzymes, 107
Glucose metabolism, 19, 104, 105
Glucose tolerance tests, 104
Glutamate, 11
Glutamic acid, 106
Glutaric aciduria, 3
Glutathione peroxidase, 234
Glycerol, 19
Glycine, 19, 104, 106, 221
Glycine:valine ratio, 106
Glycogenic amino acids, 237
Goals to reduce mental retardation, 8
Godfrey, K.M., 105, 106
Goldman, H.I., 220
Gonadotropin induced ovulation, 160
Goodenough I.Q. Exam, 213
Goodlin, R.C., 190
Gormican A. and Shrout, S., 46
Gortmaker, S.L., 176
 $G_{1,2}$ -phase in cell cycle, 25
Grieve, J.F.K., 46, 47, 58–70, 86, 92, 142, 144, 154, 224, 232, 241
Growth hormone receptors, fetus, 233
Growth period (phases) of brain, 71, 72
Growth rates
 animals versus humans, 25
 human, 239
Growth retardation, physical, 51
 severe, 129
Gruenwald, P., 17
Guatemalan studies, 22, 48, 77, 79
 and small placenta, 77
- H**
- Hague, The, 15
Hales, C.N., 113
Hallucinogens, 10
Hamlin, R.H.J., 113–115
Handicaps, permanent, 128, 212
 severe, 8, 129
Handwerger, S. and Freemark, M., 232
Harper, P.A., 179, 180
Harvard Public Health Study of 1943, 26–30
Hashish, 10
Hatjis, C.G. and Meis, P.J., 32
Hazardous diuretics, 36
Head circumference, 34, 126, 146, 212
 and birth weight, 36, 37
 and decline in mortality, 34
 in early childhood, 212
 at high altitude, 118
 and malnutrition, 126
 as proxy for intelligence, 36, 37
Head size, premature infants, 192
Hebdomadal rhythms, 238
Hellin, D., 160
Hematocrit, 141, 149
Hemoconcentration, 92
Hemoglobin, maternal, 60–62
 and birth weight, 45, 46
 and high protein diet, 60

- and iron dextran, 47
- and low birth weight, 46
- and perinatal mortality, 66
- as proxy for nutritional intake, 46, 61
- Hemoglobinopathies, 8
- Hemolysis, 76
- Hemometakinesia, 77
- Hemorrhage, obstetrical, and reading disorders, 178, 185, 186
- Hepatic dysfunction, 81, 97
- Hepatic immaturity, 107
- Hepner, R. and Bowen, M., 82
- Heroin, 10
- Hidden protein deficiency of pregnancy, 85, 86
- Hierarchy of brain structure, 75
- Hierarchy of classification, 175
- Higgins, A.C., 34-36, 194, 202
- High altitude
 - and low birth weight, 117, 118
 - and neonatal hypoxemia, 118
- High birth weight and labor, 191
- High protein diet, 59-69, 85, 98
 - with low calorie content, 70
 - maternal effects, 37-40
 - neonatal effects, 34-36
- High protein supplementation, 98
 - and hemoglobin level, 60-62
- High quality protein, 114
- High risk pregnancies, primigravidas, 142-144
- Hilbert, David, 10
- Hippocampus, 26
 - granule cells, 25
- Histidine, 106, 235
- HIV, 9
- HLA genetic factors and gestosis, 228
- Holland, starvation, 14-15, 127
- Homeostasis, moving, in pregnancy, 225
- Hormone binding proteins, hepatic synthesis, 81
- Hormone regulation of protein synthesis, 231
- Hospital based development program, 124
- Hospitalization
 - as dietary corrective, 38
 - due to low birth weight, 219
- Howard, R.C., 100
- Hughes, E.C., 89
- Human biology, 9, 223-242
- Human immunodeficiency virus, 9
- Human milk, 215
 - protein quality, 220
 - specificity for newborns, 216
- Hunger, profound effect, 13, 77
- Hunt, I.F., 47
- Hyaline membrane disease, 101
- Hydralazine hydrochloride, U.S.P., 91
- Hydramnios, 63
- Hyperactivity (hyperkinesis), relation to low salt regimens, 168
- Hyperaminoacidemia, 19, 107
- Hyperbilirubinemia, 76
- Hyperglycemia, 104, 107, 110
- Hyperinsulinism, 104
 - and gestosis, 19
 - and low pregnancy estriol, 104
- Hyperkalemia, 92
- Hyperlipidemia, 107
- Hypermedullipinemia, 84, 240
- Hypermetabolic milieu, 107
- Hyperphagia, 221
- Hyperplasia (cell number), 71
- Hypertension, 194, 196
 - definition, 89, 196
 - and hypovolemia, 97
 - and reading disorders, 184-187
- Hypertrophy (cell size), 71
- Hypervolemia, 83, 96, 97
- Hypoalbuminemia, 91, 96, 97, 121, 199
- Hypoglycemia, 91, 104
- Hypoinsulinemia, 19
- Hyponatremia, 86, 91-93
- Hypoplasia (fewer cells), 116
- Hypothalamus
 - and leptin, 204
 - vegetative functions, 221
- Hypothyroidism, 188
- Hypovolemia, 86, 92, 93, 121
 - and fetal distress, 97
 - and hypertension, 97
 - and placental perfusion, 82, 83
 - and renin, 86
- Hypoxemia at high altitude, 118, 119
- Hypoxia, 76, 118, 119, 141
- Hyttén, F. and Leitch, I., 79, 200

I

- Iatrogenic nutritional disorders, 242
- Iatrogenic sodium depletion, 90

- Ibo, The, 160
Ignorance, 76
Illegitimate births, Norway, 42
Immaturity of intestinal function, 219
Immune tolerance to fetal tissue, 225
Implantation, 224
Incongruous findings, 40
Indian studies, 93, 215
Indirect evidence for malnutrition, 116–123
Indonesian studies, 213
Industrial revolution, 206
Ineducable children, 129, 135, 137
Infancy, poor nutrition in, 210–214
Infant length, birth during starvation, 13
Infant mortality, 4
as proxy for malnutrition, 22, 144–145
Infant mortality rate, 10
and low birth weight, 5
and malnutrition, 176
during starvation, 12
in U.S., 4, 174
Infarction
hepatic, 97
periventricular cerebral, venous, 76
placental, in prematures, 81
Infection
maternal and fetal, 120
puerperal, 190
Influenza, 14, 120
Ingredients in food, xii, 18
Institutional Review Boards, United States, 58–59
Instruction about foods, 30, 199
Insulin as growth factor for fetus, 107
Insulin, exogenous, 19
Insulin levels, endogenous, 19, 107
fetal, 11
Insulin (like) growth factor-1 (IGF-1), 32, 111, 112, 237
Insulin resistance, 20, 107
in late pregnancy, 232
limited distribution, 108
Insulin response to glucose load, 20
Intellectual potential and low birth weight, 128, 136, 181
Intelligence Quotient (I.Q.) 125–141
change following improved nutrition, 212–214
in low birth weight, 127–141, 179–183
in poor infant nutrition, 210–214
in twins, 127–132
comparative, 131, 133
Intelligence testing and dietary analysis, 16, 210–214
Intensive care centers, 6, 175, 176, 205
Interchurch Bureau, 16
Intercurrent illness, 151
Intergestational menstrual interval, 151
Interleukin-1B, 82
Interleukin-10, 82
Interneural network, 75
Interobserver consistency, 146
Interpretative milieu for nutritional studies, 156–157
Interracial differences in reproductive casualty, 171–174, 179, 189–191
Intestinal resection and I.Q., 219
Intestinal tract lengths, 219
Intraobserver consistency, 146
Intravenous aminoacids, 20
Invariant stimuli, 26
Investigational design, 224
I.Q., and dietary intervention, 7, 8, 125–134
and multiple births, 125, 126, 130–133
and poor nutrition in infancy, 212–214
Ireland, birth weights, World War II, 15
Iron deficiency, 22, 47
extent of problem, 22, 149
Iron dextran, 47
Iron status, WIC children, 149
Iron supplement, 114
Isocaloric diets, 25, 38, 85
Isoleucine, 19
Isovaleric acidemia, 3
Iyenger, L., 37, 38, 50, 101
- J**
- Jamaican studies, 213
James, S.A., 207
Japan
frequency of twins, 160
post war, 17–18
Jauniaux, E., 106
Jejunoileal bypass operation, and birth weight, 31–33
Johnstone, F.D., 66–69
- K**
- Kamienzky, H., 227, 228
Kansas, Down syndrome, 184

- Kansas City, 150
 Kawi, A.A., 169, 184, 187
 Kernicterus, 8, 76
 Ketogenesis, 20, 218
 Kidney allograft and pregnancy, 240
 Kidneys, lack of role as cause of toxemia, 95
 Kindling, 26
 King, J.C., 236, 237
 Kitay, D., 199
 Knobloch, H., 115, 120–122, 141, 166, 167, 169, 174, 179, 184
 Knowledge impoverishment, 242
 Krebs cycle, 18
 Kuruvilla, A.G., 105
 Kwashiorkor, 18, 106
- L**
- Labor
 examinations during, 59
 length of, and poor diet, 193
 long latent phase, 192
 onset and protein intake, 45, 70
 precipitate, 192
 and short term fasting (Yom Kippur effect), 20
 third stage, 188
 Lactation and maternal nutrition, 13, 215–221
 educational aspects, 216
 energy cost, 217
 and menstrual interval, 22
 and premature infants, 217, 218
 and supplementation, 156, 216
 Lactogen, placental, 20, 218
 Lake County, Colorado, 118
 Lanarkshire, 183
 Langlois, P.L., 9, 190, 191
 Language development, 210
 and maternal diet, 52
 in twins, 125, 126
 Late registration of mothers, low birth weight, 34
 Latent effects
 of malnutrition, 18
 of pre-pregnancy malnutrition, 12, 125
 Latent infantile retardation, 46
 Late pediatric studies
 anomalous infants, 141
 low birth weight survivors, 127
 Late pregnancy effects, 156
 Late pregnancy supplementation effects, 184
 Learning disability, 115, 184
 Lechtig, A., 77, 78
 Length deficit, effect of, 109
 Length of infants, 14
 Length of intestinal tract, 218, 219
 Leningrad, siege of, 12
 failure of lactation, 215
 Leptin, 203
 cord levels, 204
 deficient mice, 203
 Lethal cord prolapse, 59
 Leucine, 19, 104
 kinetics (protein turnover), 111
 Leverton, R.M. and Gram, M.R., 236
 Liang, P.H., 213
 Lichty, J.A., 119
 Lilienfeld, A.M., 159–162, 164, 166, 168, 169, 178
 Lima, Peru, 117
 Limit of assimilation, 241
 Limit to fetal growth, 201
 Lipid catabolism, 21
 Lipolysis, 20, 218
 Lipotropic substances, 55
 Literature review, concerns over, 224
 Liver function, 81
 Living tissues, basic functions, 225
 Lochia, heavy, 193
 LoIudice, T.A., 32, 33
 Long, P.A., 104
 Longo, L.D., 81
 Los Angeles, 118
 Low birth weight, 8, 189
 and abruptio placenta, 189
 and anomalies, 141
 and caloric supplementation, 49
 and cerebral palsy, 159, 162
 and complications of pregnancy, 195, 239
 confounding by exclusion, low birth weight cases, 162, 196
 demographic correlates, 196
 effects of, 8
 effects of nutritional education, 41, 44, 46, 53
 effects of supplementation, 41, 45
 maternal diet, 42, 44, 46, 49, 53
 duration of programs, 36
 eradication of, 42

- and food intake, 42, 54
and inadequate nutrition, 5, 42
incidence in China, 6
incidence in U.S., 4, 6
and I.Q., 125–134
inverse relation to mental deficiency, 182
and length of gestation, 203–204
and low maternal weight gain, 200
and malformations, 141
and maternal hemoglobin, 46
and maternal weight loss, 202
and mental deficit, 127, 136, 140, 141
and multiple births, 133–134, 196
and neonatal complications, 172–173
and neurological damage, 124, 126, 135, 179, 189
and nutritional status, 120, 239
in obstetrical complications, 170–173
and permanent handicaps, 128
and physical development, 124, 129, 141
and placental weight, 79
and placenta previa, 189
and prenatal care pattern, 176–177
prevalence, 4, 31, 42
and pre-pregnancy weight, 197, 198
and protein intake, 54
and psychiatric admissions, 127
racial effects, 171–176,
rate, 175, 197
and reading disorders, 184–187
relative mortality rate, 6, 7
and respiratory distress syndrome, 140
and salt intake, 88
and schizophrenia, 127
skin of term infants, 141
and socioeconomic status, 174
in starvation, 12
and technology, 175, 176
toxemia and perinatal mortality, 104, 114
under age 18 years, 34, 88
and worst diet, 55
Lowe, C.U., 53, 201
Low maternal weight gain and low birth weight, 200
Low protein intake, 19, 20, 25
Low salt diets and diuretics, 36
Lubchenco, L.O., 119, 128, 148, 191, 195
Lung, post natal vascular flooding, 111, 112
Lysine, 106, 111, 235
- M**
- MacArthur, General Douglas, 18
MacGillivray, I., 70
Machlin, L.J. and Bendich, A., 233
MacLean, W.C. and Graham, G.G., 221
Macrosomia, 191
Main, A.N.H., 32, 33
Malformations, 144
 births during starvation, 15
 in diabetic pregnancy, 110
 at high altitude, 118
 and low birth weight, 141
 omitted from database, 41
 as poor neonatal outcome, 28
- Malnutrition
- and abrupton, 120
 and brain growth, 71–75
 and brain protein, 73
 and cognitive potential, 76
 and continuum of reproductive casualty, 175
 and developmental disabilities, 3
 and DNA of brain, 72, 74
 and gestosis, 120, 140
 and glia, 75
 and low birth weight, 120
 and childhood mortality, potentiation, 219
 and neurological development, 75
 and neurological function, 124
 and obstetrical difficulty, 192
 postnatal, 210
 and prematurity, 115
 prenatal, 3
 and respiratory distress syndrome, 101–104, 140
 and RNA of brain, 72, 74
 severe, 2, 117
 and synthesis of albumin, 97–100
- Manocha, S.L., 25
- Maple syrup disease, 3
- Marijuana, 10
- Maryland studies, 179
- Masked anemia, 10
- Maternal age and cerebral palsy, 159
- Maternal age
- general lack of relationship, 187
 under 15 years, 197
 under 18 years, 88, 227
 under 20 years, 226

- Maternal complications in low birth weight, 161–163
- Maternal death
after dermal burns, 209
decline after food supplements, 228
post thiazide, 90, 91
- Maternal fat deposition, 215
- Maternal:fetal efficacy, 21, 177, 231
- Maternal good outcome of pregnancy, 215, 224
- Maternal height, 27
- Maternal insulin sensitivity, 104, 105
- Maternal weight gain and birth weight, 132
and low birth weight, 202
and pre-pregnancy weight, 46, 200
- McGanity, W.J., 55, 56
- Mean of control data as comparison, WIC, 145, 146
- Mean weight comparisons, 43
- Medical disorders unrelated to pregnancy, 88
- Medullipin sequence, 84, 240
- Mellanby, E., 44
- Mental deficiency, 76, 167, 178, 182
in births during starvation, 16, 17
and birth weight, 178
and low birth weight, 127, 136, 140, 141
and respiratory distress syndrome, 140
- Mental function, 75
- Mental handicap, 70
- Mental hospital admissions, seasonal, 121–123
- Mental retardation, 135, 139, 140, 166, 167
and birth weight, 140, 141, 195
due to infection, 120
and maternal proteinuria, 195, 196
persistent, 214
respiratory distress syndrome, 140
seasonal, 120, 123
undifferentiated, 139
- Metabolic abnormalities in infancy, 210
- Metabolic acidosis, 220
- Metabolic cost
artificial formulas, 220
inefficient intake schedule, 237
protein metabolism, 236, 237
- Metabolic demand of pregnancy, 43
- Metabolic compartmentalization, 231–234
- Metabolic toxemia of late pregnancy, 95
- Metcoff, J., 151
- Methionine, 237
- Methylaminoisobutyric acid, 106
- 3-methylhistidine, 111
- Methylmalonic aciduria, 2
- Mexican-Americans, 207
- Mexican studies, 52, 118, 119
- Microarchitectural changes in brain
persistent, 26
- Micronutrients
antioxidant, 233, 234
supplements, 32, 47
- Microvillous plasma membrane, placenta, 105
- Military personnel and food cycles, 238
- Milk supplement, 114
- Miller, H.C. and Jekel, J.F., 150
- Miller, V., 149
- Mineral deficiencies, 95
- Mineral supplementation, 47, 114
- Minimal brain damage, 167, 180
- Miscarriage, 30, 39, 40, 166
after dermal burns, 209
frequency, 9
secondary to well water nitrate, 30
and subsequent reproductive performance, 150, 151
- Mitchell, J., 99
- Models for nutritional studies, animal, 24
- Molecular layer, cerebellum, 25
- Monozygotic twins, 125–127, 160
different birth measurements, 127
and toxemia, 228
- Montreal Diet Dispensary, 33–37, 194
- Morbidity, 12, 13
and mortality, 22, 219
- Morgane, P.J., 25
- Morris, F.H., 106
- Mortality, infant, 12, 119
and morbidity, 22
as proxy for malnutrition, 22
- Motherwell Protocol, 58–70, 78, 142–143
Aberdeen University review, 66–70
assessment methods, 59–61
birth weights, 70, 142, 143
controls, 70
dietary intake, 67–70
management of labor and delivery, 62–64
mental handicap, 182–183
perinatal deaths, 66, 204, 205

- section for failed induction, 63, 65–66, 206
surgical induction, 63–65
Motivation, maternal, 59, 144, 176
Moving homeostasis in pregnancy, 225
Muirhead, E.E., 84, 240
Multigravidae, 53
Multiple births, 178, 204
and cerebral palsy, 160
frequency in low birth weight, 134
and I.Q., 134
Multiple defects, deficiencies, 47, 128, 129
Multivariate analysis, 197
Mutual inhibition by hormones, 225
Myelination of brain, 25, 75
Myrianthopoulos, N.C., 161
Myth of pathogenesis of epilepsy, 169
- N**
- Naeye, R.L., 116, 117
Naismith, D.J., 154, 231
Nashville, malnutrition in, 56
National Academy of Sciences, 34
National Association for Retarded Citizens, 8
National Institutes of Health, 195
National Research Council, 34, 237
Natural history of disease, 138
Necrotizing enterocolitis, 219
Nelson, K.B. and Ellenberg, J.H., 169
Neonatal absorptive capacity, 218
Neonatal anthropometry, 108
Neonatal complications, 172, 173
Neonatal intensive care, xii, 104, 132, 138, 148, 175, 176
Neonatal disease and reading disorders, 187
Neonatal mortality, 15, 29, 37, 44
and cerebral palsy, 163–165
in extreme starvation, 17
in gestosis, 114
at high altitude, 118
in low birth weight, 50
relative, by diet intake, 42, 46
in WIC evaluation, 145, 147, 148
Neonatal thrombocytopenia, 91
Neonatal weight ratio, 21
Net nitrogen utilization factor (NNU), 237
Neural connectivity, 72
Neurochemical information, 75
Neurohormones, 76
Neurological abnormalities, 115, 161, 179, 180, 195
and low birth weight, 161, 180
paranatal, 161
Neurological damage, infancy, predictive value, 124
Neurological examination, reliability, 189
Neurological function, 124, 125, 181, 239
classification, 141
and maternal weight gain, 203
at postnatal age circa 40 weeks, 180, 181
Neurological impairment, 120, 124
irreversible, 214
and maternal malnutrition, 196
and maternal proteinuria, 195, 196
rate, 7, 124
Neuromuscular junctions, 25
Neurones, formation, 75
Neuropsychiatric disorders, paranatal complications, 168
Neurotransmitters, 75
New York Academy of Science symposium, 152
New York City, 118
New York State, 159
NHANES III (nutrition assessment program), 149
Nichols, B.L. and Nichols, V.N., 152, 154
Nicotine, 117
Nielsen, P.V., 218
Nigeria, frequency of twins, 160
Ninewells Hospital (Dundee), 206
Niswander, K.R. and Gordon, M., 79
Nitrates and miscarriage, 30
Nitrites, amyl and butyl, 10
Nitrogen excretion, 69
Nitrogen flux, 220, 235
Nitrogen retention, 68
Noninterventional studies, 26, 27, 30
partial, 30
Nonketotic hyperglycinemia, 3
North Carolina, 95, 96, 152, 175
Norwegian study, 41, 229–230
Norway, risk of cerebral palsy, 165
Nucleoprotein synthesis, 233
Nulliparous gravidae, uterine weight, 191
Nutrient, xii
adequacy, 153, 217
and brain development, 75
efficiency, 234–238
mediated functions, 153, 227

in WIC package, 146
 Nutrient transfer, 21
 Nutritional assessment, 108, 227
 Nutritional deficiencies or deprivation, 17, 42
 Nutritional education, 38, 47, 53, 194
 decline of nutritional deficiencies, 48
 and decline in toxemia, 193, 194
 long term, 38
 poverty level women, 47
 and protein intake, 227
 Nutritional intake, comparative, pregnancy outcome, 54, 234, 238
 efficient for growth, 154
 partition, 231–234
 Nutritional knowledge as preventative, 48
 as work in progress, 239
 Nutritional milieu, 78
 Nutritional requirements, 141, 198–199
 Nutritional research, in animals, 24
 Nutritional status prior to studies, 56
 unaccounted, 119
 Nutritional universes, differing, 65
 Nutrition in infancy, 188
 paramount factor, 210
 poor, effects of, 211–214

O

Obesity
 caloric reserves, 45
 education on proper foods, 199
 effects of fasting, 19
 and growth hormone, 237
 and IGF-1, 237, 238
 obstetric effect, 21
 and pregnancy weight gain, 199
 and protein used as energy, 45
OB gene, 203
 Obstetrical operations and cerebral palsy, 169, 178
 Obstetrical professional education, 242
 Obstetric equation, 59
 Obstetric high risk, 149, 150
 Obstetrics and Gynecology Advisory Committee, FDA, 91
 Occult water retention, 85, 86
 Ohio studies, 120–121
 Oncotic pressure of serum, 85
 Onset of labor, and neurological abnormalities, 192

following short term fasting, 20
 Ophthalmological tests, 127
 Opiates, 10
 Optimal food intake, 18, 156–157
 Optimum labor management, effect of, 178
 Ornithine, 106
 Ornithine decarboxylase, 233
 Oscillation, physiological, seven day, 238
 Oscillatory aminoacid levels, 235
 Oslo study, 41
 Osmotic pressure of serum, 85, 199
 Osteomalacia, 13
 Outcome measures, xii, 144, 147–148, 204
 diabetic pregnancy, 110
 Outcome of pregnancy
 factors in, 169
 good outcome defined, 215, 224–225
 Overweight children, 149
 Oxygen free radicals, 233
 Oxytocin, 115
 induction of labor, 64

P

Packaging of food, ingredients, 18
 Packed red cell transfusions, 60
 Pancréaticoduodenogastrectomy and pregnancy outcome, 46
 Pancreatitis, 91
 Parabiosis, 126
 Paradoxical results, 40, 46, 48–50, 78, 177
 Parasite, fetus as, 16
 Paravermis, 26
 Parietal cortex, 26
 Parity, lack of associations, 187
 Parkhurst, E., 111, 150, 159, 160, 162, 164, 169
 Partition effects, 232, 241
 Pasamanick, B., 115, 120–122, 141, 166–170, 174, 178, 179, 181, 184, 187
 Pasamanick, B., and associates, 174
 Pathological edema of pregnancy, 87, 88
 Pathophysiology of starvation, 17
 Patient originated nutritional disorders, 242
 Pattern analysis, lack of, 10, 145, 146
 Pediatric ratings, 29, 41, 100, 167
 and birth length, 28
 and birth weight, 28
 and increased serum albumin, 100
 superior health, 28–30
 Pellagra, 95

- Pelletier, D.L., 219
Pencharz, P.B., 220
Perception, aberration, 76
Perinatal care centers, 175
Perinatal mortality, 208, 209
and caloric supplementation, 50
decline in rates, 207, 208, 228
and diabetic pregnancy, 110
and diuretics, 90
and fetal activity, 109–110
in hypoglycemic preeclampsia, 104
and low birth weight, 6, 7, 37, 54, 55
low birth weight and toxemia, 115
and nutritional intake, 54, 204, 205
and physiological edema of pregnancy, 85
in preeclampsia after salt supplements, 93
primigravidas, Motherwell Protocol, 142–144
from smoking, 117
from toxemia, 114
rate, xii, 37
Periventricular infarction and neurological morbidities, 76
Persistent brain changes, 26
Peru, high altitude, 117
Pharmacological abuse, 10
Pharmacological pregnancy, 224
Phenylalanine, 19, 106, 210
Phenylketonuria, 210
Philippine study, 30
Physical condition, superior, 28
Physical growth retardation, 51
Physiological edema of pregnancy, 84, 88
and low perinatal mortality, 85
Physiological extracellular water, 83
Physiological interpretation of environmental factors, 119
Physiological stress, contradiurnal, 238
Physique, 59–60
Pike, R.L., 93
Pituitary, 115
Placenta, 77
abruption, 189
cytokines, 82
deficiency of cells, 77
dysfunction, 77
frequency of infarction, 81, 82, 87
in gestosis, 106
hypotrophy, 77
large, 79
and malnutrition, 77
in N.I.H. Collaborative Study, 79–81
perfusion and hypovolemia, 81
premature separation, 56, 189
premature separation, lack of, 100
previa, 188, 189
protein deficiency, 82
reserve capacity, 81
resynthesis of aminoacids, 105, 107
blocking of resynthesis, 107
small, 77, 79
threshold size, 79
ultrastructural lesions, 81
and vascular connections, 191
and vasoconstrictive substances, 77
villous surface area, 79
Placental
blood flow, 77, 81, 86, 111
fibrinoid, 81
function, 82, 106
growth and differentiation, 224
infarction, 81
low resistance circuit, 111
pathology, 81
transport of glucose, 105
Placental lactogen, 20, 107, 218
absence of, 218
autotrophic effect, 218
high affinity receptors in liver, 218
Placental leptin, 203, 204
Placental weight, 77–81, 83, 117
and birth weight, 79
confounding aspects, 81
effect on infant weight 6 months postnatal, 82
gigantism, 107
low weight, 78–79
puerperal weight change, 83
in preeclampsia, 72
Placentation, early, 191
Plasma proteins
immature infants, 101
as reserve, 86
Plasma renin, 84
Plasma triglycerides, 20
Plasma volume depletion, 97, 111
Platt, B.S., 9, 78
Pneumonia, neonatal, 13, 41

- Poland, 17
- Poliomyelitis, 76
- Polycythemia, 141
- Polyvitamin therapy, 43
- Poppitt, S.D., 157
- Popular press, 11
- Positive nitrogen balance, 235
- Postabsorptive state, 19
- Postnatal protein-calorie supplements, 51
- Postneonatal deaths, 13, 162
- Postpartum recovery and poor diet, 193
- Postpartum weight, immediate and birth weight, 21
- Post war rationing (World War II),
- ⁴⁰K Potassium, 236
- Poverty effects, 76
- Pragmatism in data analysis, 156, 220, 224
- Precipitate labor, 192
- Predictive value
 - early neurological testing, 181
 - of prepregnancy fatness, 21
 - of weight gain, 21
- Prednisone therapy, 218
- Preeclampsia (see also eclampsia, gestosis, toxemia), 59, 94–101
 - and hypoglycemia, 104
 - related abnormalities of fetus, 72
- Pre-edema protein depletion, 86
- Pregnancy, anabolic nature of, 21
- Pregnancy complications
 - and developmental disabilities, 161
 - and maternal hemoglobin, 46
 - and reading disorders, 184–187
- Pregnancy, good nutrition, 3
 - outcome, 68
 - successive, 51
- Pregnancy terminations, 10, 149
 - and subsequent reproductive problems, 150
- Pregnancy toxin, absence of, 95
- Pregnancy weight gain and birth weight, 197–201
- Premature birth weight, and diet, 30–38
- Premature placental separation and cerebral palsy, 164
- Prematurity, 59, 125, 147, 192
 - excluded from studies, 49
 - and toxemia, 195
 - undefined, 39
 - and underweight, 141
- Prenatal care
 - adequacy, 207, 208
 - late nutritional programs, 184
 - number of visits, 177, 207
 - so-called standardized, 176, 200
 - timing of first visit, 153, 177
- Prenatal diet and birth weight, 27–29
- Prenatal drug exposure, 209
- Prenatal maternal health, 167
- Prenatal malnutrition, 3, 24–57, 95, 98
- Prentice, A.M., 78, 154–157, 224, 241
- Pre-pregnancy weight
 - and birth weight, 45, 46, 49, 198, 200, 201
 - ideal, 21
 - low and low birth weight, 198
 - and malnutrition, 117
 - as proxy for maternal nutritional status, 117, 188
 - and weight gain, 197
- Preschool stimulation, 167
- President's Panel on Mental Retardation, 8
- Prevalence of disease, low, as confounding feature, 114
- Prevention
 - of developmental disabilities, 159, 167
 - of paranatal complications, 44, 166, 176
 - timeliness, 175
- Prevention Handbook (1974)*, 8
- Preventive obstetrics, 62
- Primates, 25
- Primigravidas, as high risk, 39, 70, 143
 - retrospective studies, 52
- Prior and subsequent infant loss, 150, 164
- Prior and subsequent pregnancy outcome, 229–230
- Private obstetricians, 37
- Proenzymes, 225
- Progeria, Gilford's, 17
- Progesterone, 20, 107
 - effect on sodium excretion, 83
 - levels, 83, 115
 - and protein synthesis, 232
 - and volume expansion, 83
- Proline, 106
- Propionate precursors, 3
- Propionic acidemia, 3
- Prospective studies, 26–52, 119
 - partial, 30
- Prostaglandins, 20, 115

- Proteins, xii
and birth length, 27
aliquots and nitrogen retention, 234–238
equilibrium, 235
for breakfast, 235–238
Protein-calorie interaction, 78
malnutrition in a vegan community, 221
in supplemental diets, 45, 50
Protein catabolism, 21, 78
Protein chemistry, 240
Protein compartments, 86, 231
Protein deficiency
and liver function, 81
occult and mental impairment in child, 86
and plasma protein, 86
and postnatal brain development, 25
Protein intake
and albumin, 85, 86
and birth length, 27
and birth weight, 27, 30–33
daily, 227, 234–238
incremental effects on birth weight, 27
index of diet quality, 54, 55
limit on absorptive capacity, 69
low, 19
maternal, 27
and miscarriage, 30
neonatal health, 28–33
objectives per program or threshold
 graded scale, 30
 68 grams, 192
 80 grams, 27, 54
 85 grams, 27, 30, 54, 55
 88 grams, 223
 90 grams, 39
 100 grams, 27
 110 grams, 42
 124 grams, 99
 260 grams, 85
as proxy for quality of diet, 54
requirements, by calculation (RDA), 34
restriction of diet, 3
threshold effect, 27
and tissue synthesis, 78
Protein, serum, 101–104
 low and respiratory distress syndrome, 102–104
Protein sparing effect of calories, 78
Protein structure, 231
Protein supplementation, 37, 39
 and birth outcome, 191
 and low birth weight, 200, 201
Protein synthesis, energy cost, 220
Protein threshold, good pregnancy outcome, 54, 55, 192, 193
Protein, total body turnover, 220
Proteinuria, 96, 104
 maternal, and developmental disabilities, 195, 196
Proteolysis, 111
Proxies for nutritional status, 117
Psychiatric hospital residence, 127
Psychological handicap, 51
Ptolemaic “logic,” 56
Public health operatives, 18
Puerperal infection, 190
Purkinje cells, 26
- Q**
- Questionable ethics, withholding food, 24
- R**
- Racial attribution of impaired cognition, 171–174
Racial bias of studies, 55, 240
Racial characteristics and nutrition, 9
Racial differential in neonatal abnormalities, 171–176
Racial distribution in population, 170
Räihä, N.C.R. and Rassin, D.K., 220
Range of healthy weight gain, 200–202, 215
Rapid weight gain, early pregnancy, 198, 199
Rate limiting step, synthesis of polyamines, 233
Reading disorders, 167, 184–187
 and paranatal complications, 185, 186
 and low birth weight, 184–186
Real age (corrected for short gestation), 129
Receptor activation, 225
Recommended Daily Allowance (RDA), 34, 45, 47, 151
Rectal examination in labor, 59
Reagan Administration and WIC evaluation, 148
Regionalized perinatal care, 176
Rehabilitative care costs, 36
Remodelling of fetal tissue, metabolic cost, 111

- Renal disease, nongestotic, 91
- Renal factors, lack of, in gestosis, 95
- Renin
 - angiotensin-aldosterone system, 84, 86
 - depression of level, 96
 - exhaustion of response, 86, 93, 96
 - secretion in pregnancy, 83, 84
- Repeat gestational age and birth weight, 229-230
- Reproductive casualty, 15
 - continuum of, 166-170
 - cultural-social-habitual-economic model, 18
- Reproductive wastage, 7
- Research Triangle Institute, 66, 145
- Respiratory difficulty at birth, 101-104
- Respiratory distress syndrome (hyaline membrane disease), 140
 - after maternal infusion of albumin, 100
 - and cord blood protein, 102, 103
 - and low birth weight, 140, 195
 - and mental retardation, 140
 - and perinatal mortality, 101-104
- Restriction of pregnancy weight gain, 223
- Resynthesis of aminoacids in placenta, 152
- Retrorenal fibroplasia, 128, 180
- Retrospective studies, 52, 119
- Retrospective vs. prospective studies, 53, 119
- Reviews of pregnancy nutrition, 242
- Richmond, S., 178
- Rickets in a vegan community, 178
- Rider, R.V., 221
- RNA, human brain, 74
- Robinson, M., 94, 194
- Rodents, 25
- Roht, L.H., 149
- Rosenbaum, A.L., 195
- Ross, R.A., 95
- Rosso, P., 21, 77, 132, 197, 200, 231, 232, 241
- Rotterdam, 15
- Rush, D., 145, 156
- Russia, World War I, 13
- Ryan, A.S., 151

- S**
- Sagan, Carl Edward, 239
- Salt, conservation, 84
 - essential substance, 87, 194
 - exhaustion of system, 96
- perinatal mortality, 87
- summer loss, 120
- Salt pork, 96
- Salt restriction, 5, 43, 92, 94
 - and diuretics, 88-92
 - and preeclampsia, 94
 - and renin-angiotensin-aldosterone system, 83-86
- Salt supplementation and birth weight in toxemia, 94, 194
- Sample size, 120, 188, 226
- Sanitation, poor, 48
- Sarcoidosis, 218
- Satiety center of brain, 221
- Schizophrenia
 - latent manifestation, 14, 127
 - and low birth weight, 127
 - birth after hot summers, 127
 - sex difference, 14
- Scleredema, 13
- Scottish studies, 46, 204, 205
- Scurvy, subclinical, 42
- Seasonal effects, 120-123, 127
 - dry season, diet, 78, 154, 158
 - eclampsia, 113
 - on mental retardation, 120-123
 - on toxemia, 113
 - wet season, diet, 78, 154, 158
- Second order ratios in data analysis, 170, 171
- Section deliveries, 144, 191, 192, 208
 - related to diet, 192, 194, 206
- Seizure susceptibility, 26
- Self assembly, 225
- Self selection bias, 55
- Semilateral position for labor induction, 63
- Semiquantitative analysis, 10
- Semmelweis, Ignaz Philipp, 10
- Senegal, 157, 158
- Sensory interrelations, 76
- Sequential perinatal loss and cerebral palsy, 163
- Serine, 26, 106, 111
- Serotonin, 221
 - receptor binding, 26
- Sex difference in schizophrenia, 14
- Shneour, E., 76
- Short term supplementation, effects, 36
- Shoulder dystocia, 191
- Significance

- bias in data, 133
problems in ascertainment, 114
use of expected values, 116
- Silber, J., 211
Singer, J.E., 202
Singleton birth, as part of good outcome, 215, 224
Singlet oxygen, 234
Skeletal muscle, 20–21, 220
Skull, defects, 13
Small for gestational age, 110
Small meals, 42
Smallness, as adaptation, 19
Small stature, 22
Smith, Clement A., 16
Smoking and birth weight, 10, 117, 148
Snyder, D.K., 238
Social factors in outcome, 227
Social neglect, 211
Social Security funds and prenatal origin of disability, 8
Socioeconomic class, 67, 68, 114, 117, 133, 225
and age of mothers, 226
and I.Q., 134, 136
Socioeconomic level and low birth weight, 179, 226
Sodium deficiency, 86
aldosterone effect, 82–86, 93
depletion, 82–86, 120
eclampsia, 92
edema in, 85, 86, 88
exhaustion of renin-angiotensin-aldosterone system, 88
first sign, impending depletion, 88
reproductive wastage, 87
and toxemia, 94
Sodium, essential substance, 87
Sodium free diet, 91
Sources of necessary information, 224
South African studies, 212
Spanish speaking pregnant women, 47
Spastic diplegia, 128
Special education and low birth weight, 129, 134
Spherocytosis, congenital, 76
S-phase in cell cycle, 25
Spina bifida, 3
Starvation ketosis, 19
Starvation and pregnancy, 12–23
differential effects, 19
Stein, Z., 16
Stickle, G. and Ma, P., 207
Stillbirth, 59
during siege of Leningrad, 12, 13
elimination by caloric supplements, 44, 50
and food intake, 39, 40, 42
in gestosis, 114
good diet, decline in, 49, 50, 114
paranatal complications, 164, 165
physiological edema of pregnancy, 85
in poor diet, 29
premature separation of placenta, 164
rate per diet success, 41, 42, 44, 46, 50
in WIC evaluation, 147
Stoch, M.B. and Smythe, P.M., 212
Strabismus, 167
Stratification of clinical data, 61
Strauss, M.B., 85, 98
Strong, S.J. and Corney, G., 160
Study
anterospective, 140
noninterventional, 26, 30
long term longitudinal, 212
prospective, 26, 37, 44, 51, 52, 120
prospective with dietary instruction, 30
retrospective, 52, 120
retrospective and prospective, comparative strengths, 53
sample size, 22, 50, 121
Stunted growth, 210
Subclinical impairment, 181
Substandard pre-pregnancy weight, 116, 117
Successive pregnancies, 51
Summer encephalitis, 120
Summer food intake, 127
Superoxide dismutase, 234
Supplementation of diet, 16, 38
in Canada, 33–35
caloric supplementation, 49
differential effects on female fetuses, 232
duration, and incidence of low birth weight, 34, 44
effects in pregnancy, 47, 48, 191–193
incomplete, effects of, 44
in Gambia, 154–158
in Guatemala, 49
high protein, 98–100
limited, 21

- liquid, 49
- in Mexico, 52
- serum osmotic pressure, 85
- in Taiwan, 52
- timing, 51
- Surface area formula, 241
- Surfactant, 241
- Survival ratios by poverty rating, 7
- Susser, M., 16
- Symbolic logic, 10
- Synapsin I, 75
- Synaptic spine density, 25, 26, 75
- Syndrome, toxemia, 96
- Synergistic effect, low birth weight and complications, 186
- Syphilis, 42

- T
- Taiwanese studies, 52
- Tanner, J.M., 219
- Taurine, 106, 111
- Taylor, J.L. and O'Leary, J.P., 31
- Technological excesses
 - latent effects, 175, 176
 - sophistication, 175
- Teen age pregnancies, 227, 237, 240
- Teff (*Eragrostis abyssinica*), 114
- Temperature change
 - and mental retardation, 120–123
 - and pregnancy gestosis, 123
 - and schizophrenia, 127
- Teratogenic action, of diuretics, 91
- Termination of pregnancy, 10
- Terris, M. and Glasser, M., 176
- Test results, correlation, 125
- Theobald, G.W., 95
- Theories, causes of toxemia (gestosis), 94–97
- Therapeutic interventions in pregnancy
 - homeostasis, 225
- Thiamine, 47, 48
- Thiazide diuretics, 89, 91, 240
 - and maternal death, 91
 - medical complications, 91
- Third trimester, critical nature, 53, 158, 174, 238
 - small meal capacity, 238
- Threonine, 19, 106, 235
- Threshold, caloric effects, 49, 50
 - placental size, 79
- stages of brain development, 71
- Thymus, small, at birth, 53
- Timor-Tritsch, I., 110
- Titus, P., 104
- Tobacco, 9
- Tompkins, W.T., 43, 44, 193, 194
- Tompkins, W. and Wiehl, D., 99, 197–199, 201
- Thomson, A.M., et al., 217
- Time structure of the body, 238
- Toronto General Hospital, 38
- Total body surface area, 209, 241
- Total parenteral nutrition (TPN), 31–33, 220
- Total peripheral vascular resistance, 111
- Toverud, G., 41, 42
- Toxemia of pregnancy
 - (see also eclampsia, gestosis, preeclampsia), 94–100
 - and angiotensin II, 84
 - and neonatal apnea, 195
 - and cerebral palsy, 164, 165
 - and dietary intake, 125, 192, 194
 - elimination by high protein intake, 98
 - due to malnutrition, 96–97, 194
 - due to salt restriction, 94
 - following diuretics, 93
 - genetics of, 228–229
 - glomerular lesions, 96
 - hepatic dysfunction, 97
 - and high salt diet, 94
 - hyperglycemia, 104
 - hyperinsulinism, 104
 - hypoalbuminemia, 97–99
 - hypoproteinemia, 97
 - iatrogenic, 56
 - kidney, not in pathogenesis, 95
 - labor induction after salt therapy, 100
 - lesions, maternal and fetal, 95
 - and mental retardation, 178
 - multiple hypotheses, 94–97
 - nonconvulsive, 85
 - nutritional deficiency state, 100
 - nutritional education, 48, 53, 194
 - and obstetric hemorrhage, 184
 - osmotic pressure of serum, 85, 86
 - pancreatic islets, 104
 - plasma volume depletion, 97
 - prophylaxis, 97
 - and reading disorders, 184, 185
 - salt restriction, 92

- and premature birth, 194
serum albumin, 97–100
as syndrome, 96
uric acid, 96
in Vanderbilt study, 55–57
and weight restriction, 199
Toxic interference with natural processes, 225
Toxicity of diuretics in pregnancy, 86, 89–94
Toxin, pregnancy, absence, 95
TPN (total parenteral nutrition), 31–33
Training, obstetric care professionals, 242
Tranquilizers, 10
Transcription of genetic factors, 225
Transfer mechanisms, placenta, 105, 106
Transfusions, blood or packed red cells, 60, 92
Transporter binding, serotonin, 26
Transporter mechanisms, amino acids, transplacental, 105, 106
Treatment of toxemia
 by high protein diet, 67, 97–100, 113, 114
 by intravenous proteins, 100
 by salt, 94, 100
Triglycerides, 20, 107
Tryptophan:neutral amino acid ratio, 221
Tuberculosis, 42
Tumor necrosis factor, 82
Twin pregnancy following radical pancreateoduodenogastrectomy, 46
Twins, 53, 54, 125
 difference in birth weights, 130–133
 discordant, 127
 frequency, 160–161
 order, lack of effect, 132
Twin studies, 125–127, 130–133
 birth weight, 130–132
 and cerebral palsy, 160
 correlation, low birth weight, socioeconomic status, 132–134
 identical, 138
 intelligence tests, 130, 133
 neurological studies, 125, 126
 relative weights, 130–132
 smaller twin, 126, 127, 130, 131
 transfusion syndrome, 126
Tyrosine, 210
- U
- Umbilical cord prolapse, 59
- Undernourishment, pre-pregnancy, 44, 199
Undernutrition, during pregnancy, 27, 198
 and brain development, 25, 26
Undernutrition during infancy, 210
Underreporting of complications, 164
Underweight births, 5, 14
Underweight mothers
 before conception, 197
 low weight gain, 116, 200
Underweight term infants, 141, 195
 and leptin level, 204
Uninsured persons, 4
United States
 incidence of low birth weight, 5, 6
 mortality, low birth weight, 6, 207
 mortality, respiratory distress syndrome, 101
 racial and ethnic diversity, 207
Unlimited weight gain, 21
Unreliable neurological tests, 125, 189
Unscientific obstetrical practices, 5, 96, 200
Upregulation, 26, 225
Urea, 11
Uric acid, serum, 96
Urinary
 estrogen excretion, 81, 100
 nitrogen indices, 68, 69
 tract infection, 196
Uterine blood flow, 92, 115
Uterine contractions, 20
Uterine growth in pregnancy, 9, 190–191
Uterine perfusion and myometrial activity, 115
- V
- Vaginal birth, part of good outcome, 215, 224
Vaginal examination in labor, 59
Validity of dietary records, 238
Valine, 19
Valman, H.B., 219
Vanderbilt Co-operative Study, 55–57
Variot's senilismus, 17
Vasoconstrictive substances, 117
 from placenta, 77
Vegan malnutrition, 221
Venesection, 96
Ventromedial nucleus, 221
Veterinary evidence, 242
Visual impairment, 179–180

Vitamin A deficiency, 43, 47, 54, 213
 Vitamin B, unspecified, 81, 154
 Vitamin B₁, 54, 114
 Vitamin B₂, 54
 Vitamin B₆, 210
 Vitamin B₁₂, 221
 Vitamin C, 96, 234
 Vitamin D, 96
 Vitamin E, 234
 Vitamin K, 42
 Vitamins in human milk, 216
 Vitamins and onset of labor, 45
 Vitamin supplementation, 99, 114, 234
 Viteri, F.E., 149
 Vocabulary tests, 126
 Volume control, gestational, 77
 Volume depletion, blood, 97
 Volume expansion, blood, 48, 84

W

Warkany, J., 141
 Wartime rationing, 53
 Warsaw ghetto, 17
 Water, hidden excess in body, 85–86
 retention, 232
 turnover in pregnancy, 232
 Waterlow, J.C., 19, 20, 237
 Wechsler Intelligence Scale, 138
 Weight control, 5, 223
 as cause of toxemia, 199
 Weight deficit, effect, 108
 Weight gain
 correlations, 215
 and evening meal, 238
 excessive, lack of fetal effect, 241
 and fetal weight gain, 198, 200
 healthy range, 200, 201
 and infant abnormalities, 202–203
 predictive value, 21
 prevention of low birth weight, 200–202
 as proxy for nutritional status, 198
 range of healthy achievement, 215

rapid, 141
 threshold, 21
 Weight, infant, and mortality, 22
 Weight:length ratio, 109
 Weight loss in pregnancy, 202
 Weight of placenta, uncritical, 82–83
 Well water, nitrates in, and miscarriage, 30
 Welsh studies, 228
 White House Conference on Food,
 Nutrition and Health, 239
 Widdowson, E.M., 217
 Wiener, G. and Milton, T., 196
 Williams, C., 236
 Williams, C.D., 18, 22
Williams Obstetrics (16th ed.), 160
 Williams, R.L. and Chen, P.M., 207
 Winick, M., 17, 72–74
 Women-Infants-Children Nutritional
 Program
 (WIC), 59, 144–154, 176, 212, 241
 admission criteria, 153
 education program, 153
 effect of neonatal care, 208
 penetrance of program, 151, 152
 World War I studies, 13, 15
 World War II studies, 15, 53, 115, 215
 Wu, H. and Wu, D.Y., 235
 Wynn, M. and Wynn, A., 4

X

X-ray pelvimetry, abandonment of, 59

Y

Yeast supplement, 114
 Yershalmey, J., 164
 Yom Kippur effect, 20

Z

Zitrin, A., 127
 Zidovudine, 9
 Zona glomerulosa, adrenal, 84, 93
 Zygote, 10

