INFORMATION TO USERS

The most advanced technology has been used to photograph and reproduce this manuscript from the microfilm master. UMI films the original text directly from the copy submitted. Thus, some dissertation copies are in typewriter face, while others may be from a computer printer.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyrighted material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each oversize page is available as one exposure on a standard 35 mm slide or as a 17" × 23" black and white photographic print for an additional charge.

Photographs included in the original manuscript have been reproduced xerographically in this copy. 35 mm slides or 6" × 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

Accessing the World's Information since 1938

300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA

Order Number 8816348

Nutritional modulation of growth and maturation and the development of specific age-related diseases: Secondary analysis of NHANES II

Levin, Laurence Buck, Ph.D.

The University of North Carolina at Greensboro, 1987

U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

PLEASE NOTE:

In all cases this material has been filmed in the best possible way from the available copy. Problems encountered with this document have been identified here with a check mark __✓__.

1. Glossy photographs or pages _____
2. Colored illustrations, paper or print _____
3. Photographs with dark background _____
4. Illustrations are poor copy _____
5. Pages with black marks, not original copy _____
6. Print shows through as there is text on both sides of page _____
7. Indistinct, broken or small print on several pages __✓__
8. Print exceeds margin requirements _____
9. Tightly bound copy with print lost in spine _____
10. Computer printout pages with indistinct print _____
11. Page(s) _____ lacking when material received, and not available from school or author.
12. Page(s) _____ seem to be missing in numbering only as text follows.
13. Two pages numbered _____. Text follows.
14. Curling and wrinkled pages _____
15. Dissertation contains pages with print at a slant, filmed as received _____
16. Other _____

_____

_____

NUTRITIONAL MODULATION OF GROWTH AND MATURATION AND THE DEVELOPMENT OF SPECIFIC AGE-RELATED DISEASES: SECONDARY ANALYSIS OF NHANES II

by

Laurence Buck Levin

A Dissertation Submitted to
the Faculty of the Graduate School at
the University of North Carolina at Greensboro
in Partial Fullfilment
of the Requirements for the Degree
Doctor of Philosophy

Greensboro
1987

Approved by

Dissertation Adviser

APPROVAL PAGE

This dissertation has been approved by the following committee of the Faculty of the Graduate School at The University of North Carolina at Greensboro.

Dissertation Adviser Lucille Wakefield

Committee Members Giles Warnick

Diane L Gill

Terry A Bazzarre

September 30, 1987
Date of Acceptance by Committee

September 30, 1987
Date of Final Oral Examination

LEVIN, LAURENCE BUCK, Ph.D. Nutritional Modulation of Growth and Maturation and the Development of Specific Age-related Diseases: Secondary Analysis of NHANES II. (1987) Directed by Dr. Lucille M. Wakefield. 177 pp.

Four age-related subsamples were selected from the Second National Health and Examination Survey (NHANES II) in order to test hypotheses involving relationships between dietary intake, method of infant feeding, rate of growth and maturation, and incidence of later life disease. Relationships between variables of interest were first placed within a comprehensive conceptual framework linking overnutrition during infancy and childhood to accelerated growth, accelerated sexual maturation, and increased incidence of later life disease.

Six hypotheses were tested in order to explore key implications of this conceptual framework. Hypotheses were grouped within three areas of analysis: (a) nutrition and growth, (b) nutrition, growth, and sexual maturation, and (c) growth, maturation, and age-related disease.

Dietary intake was observed to account for less than 10% of total variability in anthropometric (growth-related) measurements during infancy and childhood. Protein-calorie interactions were determined to be the most significant ($p = .010$, $p = .024$, $p = .117$) dietary factors in anthropometric variability. Accelerated growth in 5-8 year-olds was associated with higher protein ($p = .06$) and caloric ($p = .11$) intake than delayed growth.

Twenty-eight percent of the total variability in menarcheal age was accounted for by a combination of four dietary and two growth-related variables. Regression models combining dietary with growth-related variables accounted for greater variability in menarcheal age than models of comparable size containing either type of variable alone. Accelerated maturation was not associated with greater protein or caloric intake than delayed maturation.

Absence of subjects meeting high and low cumulative energy expenditure criteria precluded testing of hypotheses relating greater incidence of later life disease to degree of expenditure.

ACKNOWLEDGMENTS

The author wishes to express his sincere appreciation to the following people who both assisted in and made possible this research:

Dr. Lucille Wakefield, major professor, for her guidance, foresight, forbearance, and unwavering support throughout the duration of the project.

Committee members Dr. Terry Bazzarre, Dr. Diane Spitler, and Dr. Giles Warrack for their patience, open-mindedness, constructive input, and generous offering of time during the planning and implementation of research.

Frank Potter, Clifford Johnson, Dale Hitchcock, Harlene Gogan, and Bill Kallsbeek for their indispensible help with various aspects of statistical analysis.

Terri Kirchen, Judy Martin, Janet Sorel, Dr. David Pratto, Dr. David Herr, and staff members at the Academic Computing Center of the University of North Carolina at Greensboro, the Inter-University Consortium for Political and Social Research, the National Technical Information Service, the National Center for Health Statistics, and the Triangle Universities Computing Center for technical assistance in the procuring and processing of NHANES II data.

TABLE OF CONTENTS

LIST OF TABLES

TABLE Page

CHAPTER I

INTRODUCTION

Background of the Study

Relationships between nutrition and aging have traditionally been viewed from two fundamentally different perspectives. One approach has focused on aging and the impact of aging on nutritional requirements. This approach has become characteristic of an entire field of study called "geriatric nutrition" which examines age-related changes and their nutritional ramifications. The second approach has focused on nutrition and its ability to influence the aging process.

The vast majority of research efforts designed to examine effects of nutrition on aging have taken place within an experimental framework focused on the phenomenon of dietary restriction. Dietary restriction -- defined as any chronic reduction of nutrient intake which does not create nutrient deficiency (Walford, 1983) -- has repeatedly been shown to increase lifespan and decrease incidence of later-life disease in a wide variety of organisms (Armbrecht, Prendergast, & Coe, 1984; Moment, 1982). Moreover, reduction of intake has been shown to produce these effects even when its duration is limited to a

relatively small percentage of the total lifespan. When initiated relatively early in development, dietary restriction may be interrupted and even permanently discontinued without elimination of life-extending and health-improving effects (Beauchene, Bales, Bragg, Hawkins & Mason, 1986; McCay, Crowell & Maynard, 1935; Moment, 1982; Nolen, 1972; Ross & Bras, 1971; Weindruch, 1985). Despite these strong experimental links between early-life restriction and later-life phenomena, however, mechanisms underlying the overall process of dietary restriction remain unknown (Masoro, 1985a; Weindruch, 1985).

Many of the problems hampering restriction research have been conceptual in nature. One area of difficulty in conceptualization of restriction effects has been the area of human development and its characteristic processes. Researchers have often appealed to broadly-defined parameters of development as explanatory factors in food restriction experiments. For example, delayed rate of growth and delayed rate of maturation have both been widely heralded as potential mechanisms underlying nutritional modulation of aging (Masoro, 1984). But little attention has been paid to the logic behind this choice of mechanisms, or to the logical relationships between them. In 1974, while devising a method for predicting age of menarche from pre-menarcheal height and weight, Frisch argued that age of

menarche was a measure of rate of growth. From this point of view, growth and maturation were treated as inseparable parameters of development. Several years later, Glass, Harrison & Swerdloff (1979) conducted a restriction experiment "to see if the process of growth could be dissociated from sexual maturation by dietary manipulation". They reported evidence in favor of dissociation. But in neither piece of research was the significance of separability discussed, i.e., no speculation was offered as to possible advantages or disadvantages for the organism.

Underlying conceptual relationships between the process of growth and process of aging have gone equally unexplored in restriction research. Several experimenters have concluded that rate of growth, although subject to nutritional modulation, has no independent effect upon longevity or aging (e.g., Beauchene et al., 1986). Others (e.g., Yu, Masoro, Murata, Bertrand & Lynd, 1982) have argued, based on similar experimental evidence, that rate of growth is a definite determinant of length of life. But what has been absent from all such arguments has been the articulation of a comprehensive conceptual framework which addresses the issue of nutrition, development and aging not only in fact, but also in theory.

Inadequate conceptualization of developmental parameters in restriction research can be regarded as part of a broader problem, namely, inadequate conceptualization of these parameters in the field of nutrition as a whole. Since the first announcement of the recommended dietary allowances in 1943, nutritionists have appealed to loosely-defined parameters of development in their justification of macronutrient allotments. Phrases like "satisfactory rate of growth", "full realization of productive potential", and "levels most conducive to well-being" have repeatedly been used as rationale for determination of specific nutrient allowances (National Academy of Sciences [NAS], 1953, 1958, 1964, 1968, 1974, 1980). But the underlying principles which govern relationships between growth, productivity, and well-being have not been elucidated.

In several fields of study outside the realm of nutrition, conceptual relationships between diet, development, and aging have received considerable research attention. Particular progress has been made toward the understanding of these relationships in the fields of ecology, evolutionary biology, and anthropology. Nutritional modulation of the aging process has also been a topic of widespread interest in these areas.

Interdisciplinary research focused on relationships between diet, development, and aging has also highlighted the roles of protein and calorie intake in helping to determinine rate of growth, maturation, and aging (Gracey & Falkner, 1985; Heidecker, 1976; Kissinger & Sanchez, 1981; Stini, 1979a). During early life, protein and calorie intake may be closely related to method of feeding (e.g., breast versus bottle), and replacement of breast milk with commercial formula has been cited as a possible mediating factor in worldwide secular trends toward increased body size and accelerated growth (Malina, 1979; Stini, 1979a, 1981). Excessive protein and calorie intake during early life has also been linked to incidence of age-related disease at both experimental and epidemiological levels (Committee on Diet, Nutrition, and Cancer, 1982; Micozzi, 1985; Tollefsbol & Cohen, 1986; Wachman & Bernstein, 1968).

Purposes of the Study

The general purposes of the present study were three in number: first, to describe a comprehensive conceptual framework for evaluating the effects of nutrition on aging; second, to explore the implications of such a framework for developmental nutrition and for restriction research, with particular emphasis on the roles of protein and calorie intake, including their relationship to method of feeding in

early life; and third, to test the viability of such a framework through analysis of data collected on human subjects.

The Second National Health and Nutrition Examination Survey [NHANES II] was chosen as the database for testing hypotheses about a nutrition-aging framework. Conducted by the National Center for Health Statistics during the years 1976-1980, NHANES II surveyed 27,801 persons ages 6 months to 74 years who constituted a highly-stratified, multistage probability cluster sample representative of the civilian, noninstitutionalized population of the United States. The NHANES II database was made available through the Inter-University Consortium for Political and Social Research [ICPSR] in Ann Arbor, Michigan and the National Technical Information Service [NTIS] of the United States Department of Commerce in Springfield, Virginia.

Statement of Hypotheses

Elaboration of a comprehensive conceptual framework for evaluating the effects of nutrition on aging resulted in the generation of six specific research hypotheses to be tested using NHANES II. For convenience, each hypothesis was assigned to one of three interrelated sections of analysis: (a) nutrition and growth; (b) nutrition, growth and

maturation; and (c) growth, maturation, and age-related disease. Specific hypotheses were stated as follows:

Section One: Nutrition and Growth

Hypothesis 1: Protein and calorie intakes will be more closely associated with body size than fat or carbohydrate intakes.

Hypothesis 2: Accelerated growth will be associated with higher protein and calorie intake than delayed growth.

Hypothesis 3: Protein and calorie intakes will be higher in cow's milk feedings than in formula feedings, and higher in formula feedings than in breast milk feedings.

Section Two: Nutrition, Growth, and Sexual Maturation

Hypothesis 1: Combined knowledge of growth and intake will better predict age of menarche than knowledge of growth or intake alone.

Hypothesis 2: Accelerated sexual maturation will be associated with greater protein and calorie intakes than delayed sexual maturation.

Section Three: Growth, Maturation, and Age-related Disease

Hypothesis: High energy expenditure across all major channels of resource allocation will be associated with greater incidence of later-life disease than low expenditure across these same channels.

Hypothesis Testing in Relationship to Subsampling Procedures

Hypotheses in Section One were tested on two separate subsamples drawn from the NHANES II population. Subsample 1 consisted of 45 white female infants age 6-12 months who met pre-established dietary recall criteria involving normalcy of intake. Subsample 2 consisted of 276 white females ages 5-8 years who also met recall criteria.

Hypotheses in Section Two of the study were tested on a third subsample of the NHANES II population consisting of 46 white postmenarcheal females ages 11-15 years who met pre-established recall criteria involving both normalcy and recency.

Hypothesis testing in Section Three of the study involved a NHANES II subsample consisting of 46 post-menopausal white females ages 50-55 years.

Limitations of the Study

Because all secondary data analysis was carried out on white females from the NHANES II population, generalization of findings beyond this narrowly-defined group was prohibited from the outset of the study.

In addition, because extensive subject screening resulted in the extraction of very small subsamples from the total NHANES II population, confidence in

variance estimates was a matter of special concern. Generalization of findings beyond actual subsamples to the total NHANES II population must be evaluated within the context of these questionable variance estimates.

The use of cross-sectional data to evaluate a series of fundamentally longitudinal issues was another major limitation of the present study. The use of cross-sectional data prevented assessment of growth or maturation as such, since observations on each subject were obtained at a single point in time. In the absence of repeated measurements on a single individual, the processes of growth and maturation could only be quantified indirectly through the use of surrogate measurements involving body size and recalled reproductive landmarks.

Specific characteristics of the NHANES II database limited other aspects of the study as well. Exclusive use in the present study of self-reported NHANES II data meant acceptance of limitations known to accompany the use of such data. These limitations included questions of validity raised by the use of self-reported dietary recall data (Bazzarre & Myers, 1979; Campbell & Dodds, 1967; Madden, Goodman & Guthrie, 1976), as well as questions about the accuracy of self-reported reproductive history data (Danker-Hopfe, 1986; Zacharias, Wurtmann & Schatzoff, 1970). Although additional limitations of the NHANES II database

have been previously reviewed (Abraham, 1986; Forthofer, 1983; McDowell, Engel, Massey, & Maurer, 1981; Murphy & Michael, 1982), none were considered pertinent to the present analysis.

Finally, the use of a single 24-hour recall to assess habitual dietary intake meant susceptibility of results to the problem of intra-individual variability (Gardner & Heady, 1973; Liu, Stamler, Dyer, McKeever & McKeever, 1978; McGee, Rhoads, Hankin, Yano & Tillotson, 1982). Use of supplemental dietary data collected by NHANES II researchers allowed for partial remedy of this situation, since categorization of recall data as "unusual" or "part of a recent dietary change" was used as screening device for elimination of such data from subsequent analysis.

CHAPTER II

REVIEW OF LITERATURE

Although the relationship between nutrition and aging has been a topic of widespread, multidisciplinary research interest, investigation of this relationship has traditionally focused on one of two themes: the impact of aging on nutrition, or the impact of nutrition on aging. A specialized field of study called "geriatric nutrition" has developed around the first of these two themes. Age-related changes in taste and smell that effect adequacy of intake (Dye, 1984), age-related changes in metabolism that alter baseline needs (Masoro, 1985b), and age-related changes in physiological function that hamper nutrient storage, availability, or utilization (Shephard, 1986) are among the research topics which characterize this area of research Rowe, 1985; Young, 1986).

The impact of nutrition on aging is a theme which has received equal attention in the literature, but has not become characteristic of any self-contained research area. The life-prolonging effect of dietary restriction, for example, has become a phenomenon of experimental interest not only in nutrition, but in gerontology (Barrows & Kokkonen, 1982; Goodrick, 1978), physiology (Bertrand,

1983; Masoro, 1984), immunology (Walford, 1974; Weindruch, 1985) and oncology (Ross & Bras, 1971). The impact of nutrition on aging has been a topic of equal interest for anthropologists seeking to understand patterns of hominid development (Borkan et al., 1982; Stini, 1971), and for evolutionary biologists trying to account for the emergence of aging within the framework of natural selection (Calow, 1978; Hamilton, 1966; Sober, 1984). Because variation in life expectancy among contemporary human populations has been associated with nutritional factors (Borkan et al., 1982), the impact of nutrition on aging has also received attention in the field of epidemiology. The uncovering of a relationship between a population's body mass and its mean longevity (Peters, 1983; Pianka, 1978) has also spurred ecological interest in the nutrition-aging relationship.

Despite this widespread, multidisciplinary interest in nutritional modulation of aging, no comprehensive framework has emerged for assessing the process itself (Masoro, 1985a; Weindruch, 1985). The difficulty in developing such a framework has been partly methodological. Levels of analysis (e.g., molecular, cellular, organismic, populational) among disciplines differ dramatically, as do approaches to variable definition and experimental procedures. But interdisciplinary differences have not been the greatest

obstacle to development of a comprehensive framework for viewing nutritional effects on aging. That obstacle has been primarily conceptual, and has involved two specific parameters of thought: conceptualization of nutrition as a health factor in human development, and conceptualization of aging itself.

Conceptualization of Nutrition as a Health Factor in Human Development

Prevention of nutrient deficiency has been a primary consideration in the estimation of recommended dietary allowances [RDAs] since their establishment by the Food and Nutrition Board of the National Academy of Sciences in 1943 (National Research Council [NRC], 1943, 1945, 1948; NAS, 1953, 1958, 1964, 1968, 1974, 1980). However, the operative definition of deficiency has differed widely according to the type of research evidence being considered by the Board. With epidemiological types of evidence, i.e., evidence in which the clinical problems of a population have been shown to be correctable through dietary intervention, deficiency has been defined as a level of intake below intervention levels. With evidence of a biochemical nature, deficiency has been defined as sub-optimal tissue saturation or metabolic dysfunction. When physiological balance studies have been considered, deficiency has been defined as

negative balance, i.e., greater output than input of the nutrient in question (NAS, 1980).

Micronutrient Level

Despite these widely-differing definitions of deficiency, research findings have been mutually corroborative at the micronutrient (i.e., vitamin and mineral) level. In the case of niacin, for example, epidemiological evidence of deficiency as represented by increased incidence of pellagra in maize-eating countries has been reinforced by biochemical determination of "niacinogen" -- a biologically unavailable form of niacin -- in maize (Rao & Gopalan, 1984). Moreover, quantification of niacin metabolites in the urine via high performance liquid chromatography (Carter, 1982), together with metabolic studies showing diversion of tryptophan into the niacin pathway (Nakagawa, Takahashi, Sasaki, Kajimoto & Suzuki, 1973) has made possible balance study estimates of deficiency which generally correspond to epidemiology-based findings (Pike & Brown, 1984).

Macronutrient Level

At the macronutrient level, however, definitions of deficiency have been more problematic. In contrast to micronutrient research, where cellular or subcellular levels

of explanation have provided clearly-defined goals for analysis, the preferred level of explanation in macronutrient studies (i.e., studies of protein, carbohydrate and fat, or the calories which they oxidatively produce) has generally included some ambiguously-defined whole-body or developmental parameter. For example, in its 1953 discussion of the "scientific bases for the recommended dietary allowances", the Food and Nutrition Board described a "proper caloric allowance" as one which would "maintain body weight or rate of growth at the level most conducive to well-being" (NAS, 1953). "Potential improvements of growth and function" and "full realization of growth and productive potential" were the 1958 and 1964 versions of this sufficiency criterion (NAS, 1958, 1964). Ten years later came the phraseology still in use by the Board to define the developmental boundary which a protein allowance must respect: intake of protein must be sufficient "to ensure a satisfactory rate of growth" (NAS, 1974, 1980).

Within the ambiguity of these definitions lies an important set of conceptual distinctions. What rate of growth should be considered "satisfactory" or "most conducive to well-being"? What qualifies as an "improvement in", or "full realization of", growth? Should macronutrient recommendations be designed to achieve maximal rate of

growth? Should maximal growth rate be treated as an intergral part of optimal health?

Equally problematic in these developmental criteria is the omission of any specific reference to sexual maturation. Does "full realization of productive potential" include the capacity to reproduce? Does "satisfactory rate of growth" include attainment of sexual maturity within any particular time frame? What is the best way to characterize relationships between growth and maturation?

Allowance Estimation

These underlying and unresolved conceptual issues have continually posed problems for estimation of macronutrient allowances, particularly in the areas of infancy, childhood and adolescence. During the 1950's and 1960's, the desire that allowances reflect the intake of "thriving infants" and "thriving American children with relatively free access to common foods (NAS, 1958) led to several recommendations nearly twice as high as their 1980 counterparts (NAS, 1953, 1980). Some of these recommendations were actually described by the Food and Nutrition Board as being "overly generous", but were simultaneously justified on the basis of uncertainties about method of infant feeding, worldwide interest in prevention of kwashiorkor, possible prevention of tuberculosis, and lack of research-based

objections (NAS, 1953, 1958, 1964). Adolescent allowances in 1953 were not even based on actual body size, but were inferred from predicted maximum body size at maturity; as a result, recommendations climbed as high as 3,800 calories for certain 16-year-olds and 4,500 calories for certain 18-year-olds (NAS, 1953). Important conceptual distinctions about the relationship between nutrition and growth continue to be obscured by repeated reference to recommendations designed to "ensure satisfactory rate of growth" and by justification of macronutrient allowances on the grounds of ancillary benefit, e.g., "foods rich in protein, especially animal protein, are beneficial since diets high in animal protein usually contain adequate amounts of important trace nutrients" (NAS, 1980).

Conceptualization of Aging

A second obstacle in the development of a comprehensive framework for assessing effects of nutrition on aging has been conceptualization of aging itself. Like the concept of macronutrient sufficiency, the concept of aging has been difficult to define because it has harbored within it further distinctions about equally complex phenomena -- in this case, the phenomena of time and health.

The Issue of Time

Aging has been defined as a sum of changes occurring primarily in the postreproductive period which as a whole decrease the functional capacities of organisms and render death increasingly probable (Borkan et al., 1982). Implicit in this definition, and others quite similar (e.g., Comfort, 1979; Hart & Turturro, 1983; Kirkwood, 1985; Vander, 1980), has been a key temporal component: aging has associated with a particular time of life, and the passage of time has been a central ingredient in the process of aging. This time-bound aspect of aging has been underscored by the discovery of the "progerias" -- clinically-defined syndromes in which autosomal recessive traits are believed to prematurely stimulate clinical concommitants of aging. In the Hutchinson-Gilford syndrome, for example, growth failure has been shown to occur by one year of age, with loss of skin elasticity, arteriosclerosis, cerebrovascular disease and baldness occurring several years prior to death at a median age of 12 years (Borkan et al., 1982; Brown, Little, Epstein & Williams, 1978; Norwood & Smith, 1985; Schneider & Bynum, 1983).

Despite its inescapable temporal dimension, however, aging cannot be considered an inevitable consequence time and its passage. The process of aging has clearly evolved

(Borkan et al., 1982; Cutler, 1984; Hamilton, 1966; Medawar, 1952; Pianka, 1981; Sacher, 1969) and the changes that characterize senescence are known to be absent from the lives of many organisms (Borkan et al., 1982; Calow, 1978; Pianka, 1981; Wilson, 1983).

Further complication of the aging-time relationship has come from preconceived notions about the boundaries of time. As Jonas (1966) has pointed out, "the modern temper is uncongenial to the idea of immortality". We imagine time to be some abstract, all-embracing form for change (Cassirer, 1957), some endless straight line that extends as far into the past and future as we can possibly imagine. As far back as we can imagine, we imagine that there was something; as far ahead as we can imagine, we imagine that there will be something. In both directions, we imagine time to be "boundless" in its character. As a result, we have trouble picturing entities which could somehow be "exempted" from time (as were all individible entities in the mind of Aristotle, for example) (Sorabji, 1983). Although biologists have shown us that aging cannot be viewed as an intrinsic part of time's passage, isolating any set of changes from the passage of time is problematic when time has been envisioned as an all-embracing form for change.

The Issue of Health

Time has not been the only problematic component in conceptualization of aging. Equally difficult to resolve has been the underlying issue of health. As Kass (1985) has pointed out, the words "health" and "whole" have identical roots in the Old English word *hal* and the Old High German *heil*, and the historical equivalents of "health" in ancient Greek -- *hygieia* and *euexia* -- translate as "well way of living" and "good habit of body", respectively. However, as far back as the work of French physiologist Claude Bernard in the mid-nineteenth century, researchers in clinical medicine have equated health not with "wholeness" or "wellness" or "good habit of body" but with absence of disease (Ahmed, 1979; Bernard, 1865; Kass, 1985; Mechanic, 1968; Weil, 1983). Because the incidence of certain human diseases is known to undergo a large increase during the latter stages of life, and because the probability of death from certain diseases is known to increase with age, conceptualization of health as the absence of disease has relegated aging to a position of unhealthiness. "Rapid aging" has come to imply increased vulnerability to disease (Weindruch, Kristie, Cheney & Walford, 1979), and retardation of aging has become synonymous with prolongation health. Gerontologists attempting to broaden this conceptual

outlook on aging and health have been forced to coin a new term called "normal aging" in order to set the process of aging process apart from process of acquiring disease (Blumenthal, 1983), and confusion over this issue has spilled over into research on biological age where terminology has become equally confounded (Ries & Pothig, 1984).

Summary

Much of the difficultly in conceptualization of aging has stemmed from the complexity of its two key components, health and time. In the absence of clear-cut temporal and health-related distinctions, conceptualization of aging has become problematic, as has the development of a comprehensive framework for assessing the effects of nutrition on aging.

Consequences of Inadequate Conceptualization: Inconclusiveness of Restriction Research

Since the work of McCay, Crowell and Maynard in the mid-1930's, nutritional modulation of aging has been studied almost exclusively from the standpoint of dietary restriction. Dietary restriction -- also called "undernutrition", "underfeeding", "borderline nutrition", and "controlled intake" -- has been defined as chronic reduction of nutrient intake which remains unsolicitous of

malnutrition (Walford, 1983). In protozoa, rotifers, water fleas, fruit flies, fish, guinea pigs, mice and rats, dietary restriction has been shown to increase lifespan as much as 260% (Ross, 1972) and to decrease incidence of disease in later life (including incidence of glomerulonephritis, periarteritis, myocardial degeneration, mammary carcinomas, leukemias and adenomas) as much as 87% (Moment, 1982). Yet in spite of these strong experimental links between dietary restriction and life-extension or health improvement, the precise way in which food restriction generates its effects remains unknown (Masoro, 1985a; Weindruch, 1985).

Four Hypotheses

According to University of Texas physiologist Edward Masoro, four major hypothesis have dominated fifty years of thought about mechanisms by which dietary restriction alters aging (Masoro, 1984). These four hypothesis have involved (a) delayed rate of growth, (b) delayed rate of maturation, (c) reduced metabolic rate, and (d) reduced adiposity. Masoro has argued that "none of the hypotheses... appears to provide valid insight into the mechanism by which food restriction slows the aging process" (Masoro, 1984). The details of this argument turn out to be particularly interesting as commentaries on restriction research, not

only because they underscore a lack of conclusiveness in this field, but also because they reveal a certain amount of inconclusiveness in Masoro's own thinking.

Delayed Rate of Growth

With regard to rate of growth, Masoro's conclusion was somewhat at odds with his own prior statements. In a previous study, Masoro contended that while rate of growth was "probably not the major factor for the life-prolonging action of food restriction", it was definitely "a determinant of length of life" (Yu et al., 1982). This division of thought has characterized the thinking of other researchers in the field. At the University of Tennessee, Beauchene et al. (1986) have acknowledged that while growth rate has not shown significantly correlation with longevity in any of their studies, "it is obvious that body weight and/or the process of gaining it is related to longevity". Likewise, Nolen (1972) has concluded that while "it seems unlikely that rapid early growth per se has had any effect on the health or longevity of these rats", procedures which "led to an increased rate of growth and vigor during early life" also led to "increased incidence of degenerative diseases later in life". While stressing the multiple variable approach for forecasting lifespan in male Charles River COBS-CD rats, Ross, Lustbader and Bras

(1976) pointed out that four of the seven variables in their lifespan-predicting model were growth-related.

Delated Rate of Maturation

Inconclusiveness with respect to the maturation hypothesis has been equally apparent. Masoro's dismissal of maturation as an explanatory factor in restriction research was based upon his own finding that "postmaturational" restriction begun at 180 days of age was as effective in extending lifespan as "prematurational" restriction implemented at 42 days (Masoro, 1984). However, given an average menarcheal age in rats of approximately 41 days (Frank, 1976), and success by Heidecker (1976) in experimentally inducing menarche prior to 40 days of age, this designation of 42-day-old rats as "prematurational" may be open to question. Research demonstrating delay in sexual maturation as a result of dietary restriction (Glass, Dahms & Swerdloff, 1979; Glass, Harrison & Swerdloff 1976; Holehan & Merry, 1985; Merry & Holehan, 1979), when considered in conjunction with epidemiological findings linking delayed attainment of menarche in humans to decreased incidence of breast cancer (Micozzi, 1985; Schlabaugh, 1981; Sherman, Wallace, Bean & Staszewski, 1971) makes outright dismissal of a maturation hypothesis all the more questionable.

Reduced Body Fat and Reduced Metabolic Rate

In rejecting the final two hypotheses (involving reduced body fat and reduced metabolic rate), Masoro reviewed only two pieces of research -- his own 1980 study, and the work of the late gerontologist, comparative biologist, and radiation toxicologtist George Sacher. Although neither of these hypotheses has received much attention in current studies of dietary restriction, each has remained a topic of widespread interest and debate in other disciplines where nutrition and aging have been themes of research.

Search for Mechanisms

Researchers agree that inconclusiveness about the role of growth, maturation, metabolic rate and adiposity as explanatory factors restriction research must ultimately be resolved at level of biological mechanisms (Bertrand, 1983; Masoro, 1984; Weindruch, 1985; Young, 1979). But research pathways leading to the identification of such mechanisms remain unclear, and lack of success in uncovering mechanisms has been attributed to a wide variety of possible factors. Weindruch (1985) has singled out "the mysterious nature of biologic aging" and the "multitude of changes brought on by DR [dietary restriction]" as "most likely" responsible. Masoro (1985a) has pointed out the difficulty in choosing

from too many possible mechanisms, so that the search for a single solution takes on "needle in the haystack" characteristics. For Young (1979), "identification of mechanisms [has been] difficult" because mechanisms of biological aging "involve a complex set of interacting phenomenons (sic) occurring at many levels of organization".

Lack of a Conceptual Framework

Although these considerations may partially explain the lack of identifiable mechanisms in restriction research, none of them goes as far in accounting for the absence of identifiable mechanisms as the unavailability of a comprehensive conceptual framework in which to house initial hypotheses, methodologies, and subsequent findings. The problematic consequences of inadequate conceptualization in restriction research have been reflected in three specific experimental deficiencies: (a) imprecision in the establishment of baseline conditions; (b) inconsistency in the timing of restriction; and (c) inattention to relationships between rate of aging, incidence of disease, and longevity.

Establishment of baseline conditions. The terms "dietary restriction" and "undernutrition" are intrinsically comparative terms which imply some initial starting point or

baseline condition. In order for intake to be "restricted", it must be lowered down from some previous amount, taken "under" some previous level. Researchers in dietary restriction have not always been totally explicit or principled in the setting of such baseline conditions. In the work of McCay et al. (1935), dietary restriction was designed to achieve zero weight gain. In other words, the baseline condition was weight gain itself. Any animal gaining weight was not being adequately restricted according to McCay's definition. By setting weight gain as a baseline condition, McCay and his colleagues wound up with a "stairstep" experiment -- a dietary restriction pattern in which intermittent periods of weight gain were sandwiched between periods of weight constancy. But because the choice of this baseline condition was never substantiated by McCay et al., it was actually dismissed by a later researcher (Nolen, 1972) as having been "biologically unrealistic".

By far the most common reference point in studies of dietary restriction has been the condition of ad libitum feeding, i.e., that baseline condition in which the organism eats "whatever it wants". Ad libitum, or "free" feeding, involves continual replenishment of food to the organism according to its appetite, and "restricted" intake in this context means intake below the ad libitum level.

The use of ad libitum feeding as a control condition in restriction research was apparently adopted from vitamin assay methodology already well-developed by the mid-1920's (McCay et al., 1935). But in the absence of a comprehensive conceptual framework for evaluating experimental findings, unresolved issues involving rate of growth and maturation became further obscured by this choice of baseline conditions. On the one hand, ad libitum feeding carried with it the theme of maximization: an organism which ate "whatever it wanted" could be expected to maximize its potential for growth. As Nolen pointed out in his 1972 research, "ad libitum feeding is commonly used for nutritional and toxicological investigation so as not to limit the animals' growth". But at the same time, "freely" fed animals were known to experience early mortality and increased incidence of degenerative disease, i.e., submaximal lifespans and health. A restricted regime which could "support maximum reproduction, lactation and growth" while simultaneously producing maximal lifespan became the target of research (Nolen, 1972), although such a regime was not -- and has not -- been discovered. While clarification of underlying conceptual relationships between maximal growth, maximal reproduction, maximal lactation, and maximal lifespan might improve selection of baseline conditions and

formulation of restriction regimens, continued use of the ad libitum criterion (Goodrick, Ingram, Reynolds, Freeman & Cider, 1983; Masoro, 1984; Masoro, Yu, Bertrand & Lynd, 1980; Weindruch, 1985; Yu et al., 1984; Yu et al., 1982) has only postponed this clarification.

Timing of restriction. The term "weaning-intiated dietary restriction" [WDR] has been coined by Weindruch (1985) to describe the most popular time for onset of dietary restriction in experimental studies of nutrition and aging. In many restriction studies, this term has been used interchangeably with the designation of restriction as "post-weaning", and with the introduction of restricted regimens to "weanling" organisms. Yet while researchers have been consistent in their choice of "post-weaning" development as the time for onset of restriction, actual ages of "weanling" animals have been far from identical. The term "weanling" has been used to refer to SPF Fischer 344 male rats 28 days of age (Yu et al., 1982), Wistar outbred male rats 30 days of age (Beauchene et al., 1986),and to 650 Charles River COBS male rats, Charles River CD male rats, female Wistar rats, and CFY Sprague-Dawley female rats 21 days of age (Glass et al., 1979; Holehan & Merry, 1985; Merry & Holehan, 1979; Ross, 1972; Ross & Bras, 1971, 1975;). Restriction begun at 42 days of age has been categorized as "weaning-initiated" by Weindruch (1985). In

other cases, chronological age at time of weaning has simply not been specified (McCay et al., 1935; Nolen, 1972; Ross, Lustbader & Bras, 1976; Stuchlikova, Horakova & Deyl, 1975).

While the age range of 21 days produced by this listing of "weanling" studies may seem relatively narrow, it represents a significant length of time in the lifespan of these laboratory animals. Given an average lifespan of approximately 700 days (Frank, 1976), a 21-day period in the lifespan of a laboratory rat represents three percent of its total lifespan, and a period of time equal in length to total period of gestation (Economos, 1981). More importantly, the pre-pubescent growthspurt in these laboratory animals tends to occur around 35 days of age, with menarcheal age in females following an average of 6 days later (Frank, 1976). If growth and maturation are viewed as potentially important explanatory factors in nutritional modulation of aging, lack of chronological precision in application of the term "weanling-restricted" might be expected to obscure important aspects of the nutrition-aging relationship. Greater attention to underlying conceptual relationships between nutrition, growth, maturation, and health might provide better chronological guidelines for application of the term "weanling-restricted".

Defining longevity, aging, and disease. In their selection of dependent variables to measure the effects of altered intake, researchers in the field of dietary restriction have traditionally expressed interest in three distinct phenomena: rate of aging, presence of disease, and length of life. Yet in the absence of a pre-existing conceptual framework in which to place variables and their effects, the relationship between these phenomena has been difficult to clarify and continues to pose problems for restriction research.

Some investigators (e.g., Nolen, 1972) have simply lumped these phenomena together by referring to regimens which promote "the greatest long-term health and longevity". Others have limited their research to a single category of effects, for example, influence of restriction on prevalence of neoplasms (Ross & Bras, 1971) or effects of restriction on longevity (Barrows & Kokkonen, 1975; Beauchene et al., 1986). Still others have chosen to make note of the discrepancies, as have Weindruch et al. (1979) in their observation that fellow researchers use the term "rate of aging" to mean nothing more than "changed vulnerability to disease".

Like the timing of restriction and establishment of baseline conditions, depiction of aging-longevity-disease relationships requires a pre-existing conceptual framework

which has already incorporated into its parameters fundamental conceptual distinctions about nutrition, health, and lifespan. In the absence of such a framework, the "multitude of changes brought on by dietary restriction" can only continue to confound the search for mechanisms linking early-life restriction to later-life events.

Redefining Conceptual Parameters: Interdisciplinary Contributions

While the field of dietary restriction has proceeded along its fifty-year course without benefit of a comprehensive conceptual framework, research in other disciplines during this same fifty-year period has made great strides in conceptualization of parameters of key importance to the study of nutrition and aging. Overlapping research in the realm of physics, evolutionary biology, ecology, and anthropology has helped to clarify fundamental relationships between rate of growth, rate of maturation, rate of aging and lifespan. Redefinition of "health" and "healthy intake" within this context has also been attempted (e.g., Stini 1979a, 1981a). While no single piece of research can be singled out as "most significant" in the above-mentioned process, multidisciplinary interest in one issue has been particularly strong. That issue -- dating back almost 150 years and regarded by some as perhaps

the key issue in the history of physics (e.g., Campbell, 1982; Rifkin, 1980) -- is the issue of entropy.

Physics and Entropy

First used by the German physicist Rudolf Clausius to describe the unavailability of energy, the term "entropy" has long been associated with the Second Law of Thermodynamics. (The principle of the Second Law had actually been recognized by French physicist Sadi Carnot some twenty-six years earlier (Rifkin, 1980). As articulated by Monod (1971), the Second Law states that "within an energetically isolated enclosure all differences of temperature must tend to even out spontaneously." The tendency of thermal differences to spontaneously "even out" had practical implications for Carnot in his efforts to understand the workings of steam engines (Asimov, 1966). But the theoretical implications of Second Law extended well beyond the realm of thermodynamics. For physicists, the tendency of energy differences to "even out" meant that orderliness in the unverise must forever be diminishing, since order was nothing more than an arrangement of energy differences (Romer, 1976). If all energies were destined to "even out", like ice cubes melting in a glass of water, the ultimate condition of the universe had to be one of disorder. Thus, the Second Law became the law of "time's

arrow", pointing in the direction of universal disorder (Blum, 1968; Romer, 1976).

The spontaneous evening-out of energy described in the Second Law also implied an inevitable wastefulness. "Disorderly" energy was the same as useless energy, energy that was difficult to harness and convert into beneficial forms. For example, it was easy to break an egg into dozens of disorderly pieces, but nearly impossible to reassemble the shell into its original, orderly form. Disorderliness meant wastefulness and uselessness, or in the words of Clausius', "unavailable energy". It was this tendency toward disorderliness, unavailability and uselessness that Clausius designated with the word "entropy".

Although originally referenced to the workings of heat engines, the concept of entropy has recently been exported from the realm of thermodynamics to a wide range of human endeavors. Rifkin (1980) has interpreted soil erosion and environmental pollution as manifestations of entropy; Brooks and Wiley (1984; 1986) have focused on entropy as the key ingredient in evolution; and several theorists have found critical roles for the concept of entropy in the field of cybernetics (Campbell, 1982; Monod, 1980). In the sciences, measurement of entropy has also won critical acceptance. Entropy of transition, a four-term

algebraic equation, has become a routinely measured thermodynamic property of elements and oxides (Weast, 1985). Molar entropy has been defined as Avogadro's number times Boltzman's constant times the natural log W, where W is the number of ways of arranging a system without changing the internal energy (Zubay, 1983). Organizational entropy (Sacher, 1967), organic entropy (Hershey, 1980), and macroscopic entropy (Hershey, 1963) have also been mathematically defined.

Entropy and aging. Attempts to describe the process of aging as a function of entropy (Lotka, 1922, 1945; Sacher, 1959; Szilard, 1959) have focused on the observation that metabolic rate in homeothermic mammals is inversely related to lifespan (Sacher, 1967). In other words, for small mammals like the shrew, with heart rates of 1,000 beats per minute, daily metabolic expenditure is extremely high and lifespan (approximately two years) extremely short (Lindstedt & Calder, 1981; Economos, 1981). For large mammals like the elephant, these conditions are reversed: metabolic rate is relatively low (e.g., only forty heartbeats per minute), and lifespan relatively long (about sixty years). Multiplied together, heart rate and lifespan have been observed to produce a near biological constant: 40 beats per minute times 60 years of life equals 1.26 billion beats, and 1,000 beats per minute

times two years of life equals 1.05 billion beats (17% less, but still remarkably similar). In other words, "measured by their own internal clocks, mammals of different sizes tend to live for the same amount of time" (Gould, 1980).

Viewed from the standpoint of entropy, high metabolic expenditure also means high energy waste. Since all energy-requiring processes move in a disorderly, "wasteful" direction, a heart beating 1,000 time per minute can be expected to produce 25 times as much "waste" (i.e., entropy) as a heart beating 40 times per minute, that is, only 1/25th as fast.

"The production of entropy concommitant with metabolic activity" has been proposed as a definition of the aging process itself (Sacher, 1967). When defined in this way, aging becomes a by-product of "inappropriate" exergy expenditure -- "inappropriate" in the sense of metabolically unsupportable or poorly-conducted in a thermodynamic sense:

> [It is] ... not growth per se but its excess above or lagging behind the level supportable by the metabolic processes of an organism [that] determine (sic) the organism's life span. (Economos, 1981)

> Aging can no longer be considered as simply a question of how much metabolic work: it is also a function of how well the work is done, in thermodynamic and informational terms. (Sacher, 1967)

These entropy-based definitions of aging suggest three basic goals for organisms in which aging takes place: (a) coordination of fundamental life processes in such a way that metabolic capacities are seldom underdeveloped or overextended; (b) alteration of fundamental life processes when imbalance does occur; and (c) development of "counter-entropic" mechanisms. Pursuit of the first two goals has been studied most closely in ecological analyses of resource allocation and will be examined in the upcoming section of this review. Economos (1981) has pointed out that organismic activity directed toward the third of these goals (development of "counter-entropic" mechanisms) has been neglected in some theories of aging based on entropy:

> The rate of living theory emphasized only the rate of entropy accumulation (increase of disorganization) assuming it to be proportional to the rate of biochemical processes in the organism, i. e. , proportional to specific metabolic rate. However, life span would be necessarily proportional to this rate of living only in simple machines or animals whose counter-entropic mechanisms (such as all kinds of repair at all levels, antioxidant protection of sensitive cellular components, etc.) were exactly the same .... This assumption is not valid in sophisticate machines, let alone in animals.

The range of counter-entropic mechanisms (particularly enzymatic antioxidants) differentially available to organisms has been recently reviewed by Cutler (1979, 1984).

Theories of aging based on the concept of entropy have contrasted sharply with "senescent gene" theories in which aging has been regarded as a genetic imposition, i.e., part of nature's evolutionary design (Sacher, 1982). According to an entropy-based approach, organisms are not designed to age; instead, "organisms age as a result of the way that they are designed to do other things" (Calow, 1978).

The "other things" that organisms are "designed to do" are none other than fundamental processes of life: growing, maturing, reproducing, and simultaneously staying healthy. These processes are viewed as basic channels for energy expenditure in organisms. Overinvestment in these processes means overexpenditure of energy, which in turn means overproduction of entropy and accelerated rate of aging. While theories of aging based on entropy have emphasized the importance of these energy-expending processes (cf., Brooks & Wiley, 1986), nowhere have they been more closely examined than in the field of ecology and its subspeciality, resource allocation.

Ecology, Evolutionary Biology, and Resource Allocation

The idea of "resource budgets" has been proposed by Pianka (1981) as a means of consolidating thought about the

wide range of energy-requiring activities conducted by living organisms. Growth, maturation, reproduction, tissue maintenance and repair -- "these activities cannot be dealt with adequately in isolation since they usually make conflicting demands on an animal's finite resources" (Pianka, 1981). For example, if energy is devoted to growth it becomes unavailable for reproduction, and unless increasing size has a significant impact upon fecundity or competitive/survivorship ability, this "budgeting" of resources may turn out to be short-sighted (Pianka, 1981).

Energy budgets and life history strategies. In the fields of ecology and evolutionary biology, general agreement has been reached about the central components of an energy "budget". Organisms tend to expend their energy on one of four basic activities: (a) growing, (b) maturing, (c) reproducing, and (d) staying healthy (Austin & Short, 1982; Bronson, 1985; Brooks & Wiley, 1986; Calder, 1984; Calow, 1978; Delaney, 1982; Edlin, 1976; Millar & Zammuto, 1983; Peters, 1983; Pianka, 1978, 1981; Roff, 1986; Stearns, 1976; Townsend & Calow, 1981; Wilson, 1983;). Because all organisms are limited in their ability to procure, store and process food, they operate on limited energy budgets and are constantly forced to make trade-offs and compromises among conflicting energy demands (Pianka, 1981). These trade-offs and compromises have been used to explain the wide variety

of life history strategies found among homeothermic mammals (Bronson, 1985; Millar & Zammuto, 1983; Stearns, 1976), as well as to account for phylogenic patterns in mammalian (and nonmammalian) evolution (Gould, 1977). The evolution of scrotal reproduction (Cowles, 1965; Setchell, 1978), hibernation, hypothermia and torpor (Cranshaw, Moffitt, Lemons & Downey, 1981) and embryonic diapause (Short, 1982) have also been interpreted from this "energy trade-off" perspective.

Calder (1985) has pointed out that "for any given body plan and size, there is a range of trade-offs". These trade-offs have been mapped out for a wide variety of plant and animal species (e.g., Bronson, 1985; Calow, 1979; Clutton-Brock, 1982; Delaney, 1982; Edlin, 1976; Pianka, 1981; Wilson, 1983). Small herbivores sleep longer than large ones to help offset the high energy demands of rapid metabolism (Peters, 1983). Cottontail rabbits living in the southern United States respond to the low-energy demands of climate with continuous, year-round breeding, while their counterparts in the northern U.S. try to offset greater climactic demands by curtailing litter production to three or four times a year (Bronson, 1985). Moreover, this notion of trade-offs seems equally applicable at the population level. In growing populations, for example, age

at first reproduction tends to get "pushed" to the physiological minimum, since under conditions of population growth, like conditions of compound interest banking, "it will always pay to get your money in the bank as soon as possible" (Stearns, 1976). In declining populations the opposite event takes place: age of first reproduction gets postponed in order to slow the rate of population decline (Stearns, 1976).

r and K selection. The analysis of resource allocation at individual and populational levels has perhaps most clearly manifested in the concept of "r" and "K" selection. According to this concept, organisms differing in body size approach survival in different ways. "r" strategists, small in size, and often forced to exploit unpredictable environments, take a "boom or bust" approach to their existence. A life history profile of these "r" strategists typically reveals short gestation, large litters, short birth intervals, rapid sexual maturation, and short lifespan. "K" strategists, on the other hand, larger in size and constantly trying not to overload the carrying capacity of their environment, have life history profiles which feature long gestation, single offspring, long birth intervals, slow sexual maturation, and long lifespan. (May & Rubenstein, 1982; Short, 1982).

Heterochrony. Gould (1977) has used the notion of trade-offs to extend the analysis of life history strategies to the process of evolution itself. In his clock model of heterochrony, Gould (1977) sets forth three fundamental processes as "realms of dissociation" -- "independent vectors operating during the lifetime of an organism" which can be phylogenically "reset" to prevent extinction of a species. This "resetting" or "dissociation" is viewed as analogous to the disengagement of gears:

> The fundamental processes are seen as constituting a perfectly integrated whole. They fit in with each other in such a way that the final product comes into being .... But ... they can be dissociated experimentally or thrown out of gear with one another. (Needham 1933)

Gould's three "realms of dissociation" involve (a) shape, i.e., the form, structure, morphology, proportionality or allometry of the organism; (b) size; and (c) rate of maturation. Displacement of any one realm from its ancestral relationship with the others can alter the course of evolution.

For Gould, the response of aphids to discovery of an uncolonized leaf is an excellent example of heterochrony at work. For aphids, an uncolonized leaf represents a superabundant resource "up for grabs". At least momemtarily, it eliminates the need to explore other environments or worry about population overexpansion. The aphids respond

to this opportunity by producing a wingless generation of offspring: a generation that not only starts out wingless, but actually maintains this juvenile form throughout adulthood. The temporary elimination of wings makes it possible for aphids to shorten their maturational cycle; and by accelerating sexual maturation relative to somatic development, they can better exploit the uncolonized leaf by reproducing more quickly. Tactile stimulation following crowding serves as a cue to return to wing production (Gould, 1977).

Summary. Aanalysis of energy trade-offs at the individual, populational, and evolutionary level has made it clear how "poor budgeting" and "misdirected funds" can upset biological development. But what has emerged less clearly is the relationship between unbalanced resource allocation and that special aspect of biological development known as "aging". Research in the field of anthropology has helped to clarifiy this relationship by looking at nutrition and health in man and his anthropological predecessors from the standpoint resource allocation.

Anthropology, Neoteny, and Aging.

The comparison of man to other primates -- and even to his more recent hominid progenitors -- has revealed striking trends in development which anthropologists and

biologists have classified under the heading of "neoteny" (Cutler, 1984; Gould, 1977; Stini, 1975). Neoteny has been defined by Gould (1977) as "the retention of formerly juvenile characters by adult descendants through retardation of somatic development". Researchers in this area have observed that adult humans look strikingly similar to their pongid relatives, e.g. chimpanzees or orangutans. But adult humans do not look similar to adult chimps or orangs. They look similar to these pongids in their juvenile stage of development, as if in the course of evolution, the change from juvenile to adult shape had been somehow "left out". Such a phylogenic omission is thought to have been possible given neoteny, i.e., a slowing down of "shape-change" relative to "size-change" and rate of maturation.

The development of form is not the only process which appears to have been slowed down in the evolution of homo sapiens. Retardation across all parameters of development has been shown to be a key factor separating man from his fellow primates. Otis and Brent (1954) have looked at the appearance of more than one hundred developmental "stage marks" and have found that humans take 2-4 times longer than other primates to reach early stages of development, and 5-15 times longer to reach later developmental stages. Man

reaches puberty at 60% of his final body weight; the comparable percentage for chimpanzees falls between 50-60%, and for most laboratory and farm animals, around 30% (Bryden, 1968). The rhesus maccaque achieves 65% of its final cranial capacity by the time of birth; the chimpanzee, 40.5%; and man, only 23% (Gould, 1977). In chimpanzees, chest circumference surpasses head circumference 35 days after birth, but in humans, this event does not occur until the second year of life (Catel, 1953; Lowrey, 1986).

This slowing down of human development has also been linked to the need for prolonged extrauterine care (i.e., "secondary altriciality") which is characteristic of the newborn infant and which might play a key role in the establishment of unique bonds between parent and child (Cutler, 1984; Gould, 1977). Developmental retardation has also been linked to the juvenilization of behavior which typifies human play (Campbell, 1982). Prolongation of interuterine brain development into postnatal life may also have permitted the occurrence of more complex forms of learning in human beings (Campbell, 1982).

Secular trends. Given the widespread importance of delayed development in the evolution of human beings, it is not surprising that trends in the opposite direction during the past hundred years have caught the attention of anthropologists. Stini (1979a) has summarized these trends as

four in number: (a) a trend toward increased human body size; (b) a trend toward accelerated rate of growth; (c) a trend in females toward earlier attainment of sexual maturity; and (d) a trend toward increased lifespan.

Secular trends toward increased body size and accelerated rate of growth during the past century have been a topic of widespread research interest (Himes 1979; Lowrey, 1986; Malina, 1979; Meredith, 1963; Roche 1979; Stini, 1979a, 1981a; Tanner, 1968, 1986), as have parallel secular trends toward earlier age of menarche (Bullough, 1981; Burger & Gochfeld, 1985; Danker-Hopfe, 1986; Frisch, 1978; Golub, 1983; Jafarey, Khan & Jafarey, 1970; Lowrey, 1986; Malina, 1979; Stini, 1979a, 1981a; Tannner, 1968, 1986; Zacharias et al., 1970). While the precise magnitude of these trends has remained a matter of debate, an increase in adult stature of at least one half centimeter per decade (Roche, 1979) and an advancement of menarcheal age by a minimum of one year (Tanner, 1981) have been widely acknowledged. Based on data reported by Meredith (1976) and Tanner (1968), acceleration of growth rate, while varying with the anthropometric dimension under consideration, has averaged a minimum of one month per decade.

Less debatable has been the trend toward increased human lifespan. In the United States, life

expectancy at birth (for both sexes combined) has increased by 25 years (or 55%) since the turn of the twentieth century (Stini, 1979a). Fifty percent survival rate in the U.S. has also increased by 50% during this time (Walford, 1983).

Question of maladaptiveness. University of Arizona anthropologist William Stini has raised the question of maladaptiveness with respect to this combination of trends:

> People are getting bigger earlier and, at least in the case of females, are lengthening their potential reproductive lifespan.
>
> There is good reason to question the desirability of artificially stimulated growth ....
>
> Overabundant nutrition during early growth and development yields an adult whose body size is at or close to the maximum for that genotype. While this is maximization of growth, it is a mistake to call it optimization. There are evolutionary theories ... to support this. (Stini, 1979a)

One of the "long-term evolutionary trends" that has shaped human requirements is neoteny, and from the standpoint of neoteny, the question of maladaptiveness seems appropriate. In a species whose evolutionary emergence has depended on delayed rate of growth, maturation and morphological change, acceleration of these developmental parameters stands out markedly.

The question of maladaptiveness appears even more legitimate when the issues of entropy and resource allocation are brought into consideration alongside these evolutionary events. Accelerated growth, accelerated

maturation, increased body size, and increased lifespan represent additional energy costs to the organism, and from the standpoint of thermodynamics, increased entropy production. They also represent a cost increase which cuts across three of the four basic channels of resource allocation: growth, maturation, and maintenance of body mass. This particular pattern of expenditure constitutes a use of resource allocation channels not ordinarily seen in life history analysis. "r" strategists accelerate maturation, but decrease body size and lifespan; "K" strategists increase body size and lifespan, but delay maturation. There is no life history strategy in which accelerated maturation occurs simultaneously with increased body size and lifespan.

The Principle of Compensatory Change

The combination of activities described above may be at odds with the principle of "compensatory change", which Brooks and Wiley (1986) have used as a basis for interpreting evolution as a manifestation of entropy:

> Any successful innovative change in any developmental program is accompanied by a countering, compensatory, change in all or part of the rest of the program.

> For example, the termination of growth and differentiation is often highly correlated with the initiation of reproductive activity. Likewise, organisms that are small, with relatively short developmental periods, have high metabolic and reproductive rates ....
>
> ... ecological capabilities, as important as they are to the biology of the species, are effects, or emergent properties, of compensatory developmental changes ...

The principle of compensatory change points out the necessity of biological "trade-offs", and recalls the observation of Gould (1980) that -- at least as far as mammals are concerned -- all organisms are allotted the same amount of biological time in which to carry on fundamental life processes. Length of life is scaled to pace of life (Gould, 1980), and is partially determined by the amount of energy which gets allocated to growth, maturation, maintenance of body size, and reproduction. When life processes happen "too quickly", i.e., with disregard to the rate of activity supportable by the organism (Economos, 1981), the usual result is compensation via curtailment of lifespan. But what happens if lifespan turns out to be "unavailable" for curtailment? What happens if breakthroughs in medical research and improvements in the provision of medical care continue to foster greater longevity and percent survival? In other words, what happens if length of life cannot be scaled down when pace of living speeds up?

Compensatory Change and Compromised Health

According to conclusions reached by Stini (1979a, 1981a) and Morrision (1984), "what happens" may be compromised health:

> Over the last century, there has been a significant increase in human life expectancy in many parts of the world. At the same time there has been a trend toward increased body size ... there is reason to suspect that maximization of human growth has detrimental effects ... [it] may predispose the individual to certain degenerative conditions... (Stini, 1979a)

> It may be that, as far as nutritional manipulation is concerned, full youthful vigor is incompatible with a healthy ripe old age. If we want a lot of one, we may have to settle for a bit less of the other. (Morrison, 1984)

These very general statements about predisposition toward "degenerative conditions" and "a bit less" health in later life describe the possible results of a maladaptive life history strategy from a theoretical standpoint. But the theoretical effects of a maladaptive life history strategy (i.e., a strategy which combines accelerated growth and maturation with increased body size and longevity) have been shown to correspond with actual findings in one specific area of disease research: the epidemiology of breast cancer.

A recent review of findings in this area of research (Micozzi, 1985) has concluded that dietary patterns in early life have lasting effects upon rate of growth and maturation, and that these nutrition-mediated factors are in

turn related to later-life risk of breast cancer. Moreover, these interrelationships can be quantified through the use of anthropometric and dietary measurements:

> Dietary patterns early in life have lasting effects on growth, including maximum attained height, body size, body composition, and other nutrition-mediated variables, which can be measured in adults. Variables such as weight, height, age at menarche, and fertility are nutrition-mediated factors which have been studied relative to breast cancer risk ... Distinct patterns of nutrition at different times in life may be the common link among body size, age at menarche... and the risk ofbreast cancer in women. (Micozzi, 1985)

A nutritional basis for reduced risk of breast cancer via developmental retardation has also been described, with certain practical reservations, by Willett (1987):

> ... energy restriction (perhaps necessary early in life) sufficiently severe to reduce stature [may reduce] risk of human breast cancer.
>
> If [this] hypothesis is correct, it probably has no direct implication for cancer prevention in this country ... It seems a remote likelihood that an affluent society such as ours will voluntarily restrict its energy intake to the point of stunting its children ... (Willett, 1987)

Summary

As a result of overlapping research in the fields of physics, evolutionary biology, ecology and anthropology, a comprehensive conceptual framework has been made available for evaluating the effects of nutrition on aging. The emergence of this framework has been the result of research progress in accomplishing four specific conceptual tasks:

Clarification of the aging process. By systematically addressing the notions of time and health which serve as the basis for conceptualization of aging, entropy research (originating in the field of physics) has provided a basis for comprehensive re-evaluation of the aging process. Central to this re-evaluation has been rejection of "obligate aging" in favor of a "by-product" approach which claims that organisms age, not by evolutionary mandate, but as a result of the way they were designed to do other things.

Specification of relationships between developmental processes. The "other things" that organisms were "designed to do" have been closely analyzed by evolutionary biologists and ecologists interested in the process of resource allocation. Treatment of growth and maturation as independent parameters of development has been a consistently important feature of this analysis.

Elaboration of principles governing development. Conformation of developmental events to the priciple of compensatory change has been a central concept in the analysis of life history strategies, as well as in the recognition of phylogenetic patterns of development. Incorporation of a lifespan parameter into this theory of biological "trade-offs" has made it possible for evolu-

tionary biologists and ecologists to address inter-relationships between development, aging, and longevity.

Consideration of aging within a specifically human context. Comparison of man to other primates in the field of anthropology has allowed re-interpretation of secular trends in human developement from a standpoint unique to man. The specific configuration of current secular trends -- which consists of accelerated growth and maturation in combination with increased body size and lifespan -- has emerged as potentially maladaptive given the history of man's emergence as man. By addressing the possibility of compromised health and accelerated aging in later life within this context, anthropologists and epidemiologists have helped to incorporate a specifically human parameter into consideration of relationships between nutrition and aging.

Implications for Conceptualization of Nutrition as a Health Factor in Development

As discussed earlier in this review, definitions of deficiency at the macronutrient level -- definitions which have been central to the establishment of recommendations -- have been problematic for the Food and Nutrition Board of the National Academy of Sciences throughout its forty-year history of dietary recommendations. The

conceptual framework outlined above has direct implications for macronutrient recommendations and for determination of macronutrient deficiency.

Reassessment of Maximization Criterion

"Full realization of growth" (NAS, 1958, 1964), "predicted maximum body size at maturity" (NAS, 1953), and "thriving American children with relatively free access to common foods (NAS, 1958) are brought into question as appropriate criteria for determination of macronutrient intake, since these criteria fail to address the potentially maladaptive nature of growth maximization within the context of other increased energy expenditures. The goal of "ensuring a satisfactory rate of growth" (NAS, 1980), while not directly stating a criteria of maximization, is also brought into question as failing to address this basic issue.

Increased Attention to Protein and Calorie Intakes

A further implication of the previously-described framework is a need for increased attention to macronutrients most directly involved in the modulation of fundamental life history processes (growth, maturation, reproduction, and body size maintenance). Among all individual macronutrients, the roles of protein and calorie in support of basic life history processes remain most

clearly articulated across widely-differing levels of research. The role of caloric intake in meeting energy requirements of developing organisms is virtually self-explanatory and clearly related to all four processes listed above. Although the role of protein intake in life history processes is equally obvious from the standpoint of biological function (i.e., enzymatic reaction, nutrient transport and storage, structural support, immunological defense, etc.), relationships between protein intake and rate of growth have also been explored at the hormonal (e.g., Daughaday, 1981; Martin, 1985), and epidemiological (e.g., Gracey & Falkner, 1985; Stini, 1979a) level. Relationships between protein intake and rate of sexual maturation have been equally well-researched (e.g., Burrell, Healy, & Tanner, 1961; Heidecker, 1976; Kissinger & Sanchez, 1981; Kralj-Cercek, 1956; Sanchez, Kissinger & Phillips, 1981).

The uniqueness of protein intake from the standpoint of a life history framework has been further evidenced by interdisciplinary research relating protein intake to longevity, rate of aging, and incidence of age-related disease. At the subcellular level, decreased protein synthesis following dietary restriction and subsequent

retardation of informational (genetic) transfer has been cited as a possible mechanism for extension of lifespan through retardation of development (Barrows & Kokkonen, 1975; Tollefsbol & Cohen, 1986). Negative effects of high protein intake on calcium retention (Allen, Oddoye, & Margen, 1979; Anand & Linkswiler, 1974; Wachman & Bernstein, 1968) and correlations between high-protein diet and incidence of osteoporosis (Ellis, 1972) have raised questions about protein intake in relationship to age-related losses in bone density. The role of high protein intake as an independent risk factor in development of certain cancers (cf., Micozzi, 1985; Committee on Diet, Nutrition, and Cancer, 1982) has also been reviewed.

One significant shift away from the focus on protein and calories as modulators of life history processes, however, has been attention to the role of fat in attainment of sexual maturity and reproductive capacity. As a possible etiological factor in attainment of menarche and reproductive capacity, the role of fat deposition has received widespread attention in nutrition research (e.g., Billewicz, Fellowes & Hytten, 1976; Cameron, 1976; Danker-Hopfe, 1986; Frisch, 1974, 1978; Frisch & Revelle, 1970; Golub, 1983). Given a minimum energy requirement of approximately 80,000 calories to sustain healthy pregnancy

and lactation (Pike & Brown, 1984), and the uniqueness of adipose tissue as an energy repository, the extensiveness of fat deposition has become a logical consideration in assessment of menarcheal age and reproductive capacity. Frisch (1983) has reviewed possible mechanisms linking adiposity to the arrival of menarche, and these mechanisms include a) altered rate of conversion of androgens to estrogen, b) re-direction of estrogen metabolism, and c) altered capacity of serum hormone binding globulin, producing altered concentrations of free serum estradiol, and availability of estradiol to brain and other target tissue. Still, the role of adiposity in attainment of menarche has remained unclear since the behavior of many adiposity indicators (e.g., weight-for-height and skinfold measurements) has suggested that body composition is not a primary trigger of this maturational event (Billewicz, Fellowes, & Hytten, 1976; Cameron, 1976).

Implications for Restriction Research

As discussed earlier in this review, three specific problems in restriction experiments can be viewed as consequences of initially inadequate conceptualization of nutrition-aging relationships. These experimental problems

include (a) establishment of baseline conditions, (b) timing of restriction, and (c) differentiation of later-life events. The previously-described conceptual framework has implications for the resolution of all three experimental difficulties.

The baseline condition of ad libitum feeding -- because it carries with it a theme of maximization -- is shown to be inappropriate as a parameter in animal-model research if results from animal-model findings are to be extrapolated to humans. A need is indicated for alternatives to the ad libitum model in which baselines are set at optimal (versus maximal) levels.

A need is also indicated for restriction onset to be carefully timed with respect to both growth and maturational parameters of development, since growth and maturation appear to function as independent channels of energy expenditure. Unless it goes on to clarify levels of somatic and sexual development, the designation of animals as "weanling restricted" cannot provide a solid framework for interpretation of experimental findings in restriction research.

The conceptual framework described above also suggests that measurement of later-life events in restriction studies be based solely not solely on disciplinary interests, but

also on underlying principles governing lifespan and its components. The confinement of research to a single category of effects, or the lumping together of later-life phenomena under some all-encompassing heading [e.g., "greatest long-term health and longevity" (Nolen, 1972)] appears inadequate as a foundation for increased understanding of restriction effects.

Generation of Research Hypotheses

On the basis of the conceptual framework described above, several hypotheses were formulated with respect to nutrition-aging relationships. For convenience, these hypotheses were grouped together in three sections according to three interrelated themes: (a) nutrition and growth, (b) nutrition, growth and sexual maturation, and (c) growth, maturation, and age-related disease. Specific research hypotheses and rationale behind their formulation are presented below under appropriate sectional headings.

Section One: Nutrition and Growth

Hypothesis 1: Protein and calorie intakes will be more closely associated with body size than fat or carbohydrate intakes.

Hypothesis 1 was designed to test the relative importance of dietary protein and calorie contributions to

rate of growth. If these intake parameters were unique in their ability to modulate nutrition-growth relationships, their contribution to explained variability in growth-surrogate measures should also be unique in magnitude.

Hypothesis 2: Accelerated growth will be associated with higher protein and calorie intakes than delayed growth.

Even if protein and calorie intakes did not turn out to be unique modulators of growth rate, accelerated and delayed growth might still be associated with high and low levels of intake. Expressed somewhat differently, although rate of growth might reflect level of intake across many dietary parameters, levels of protein and calorie intake should still be consistent with overall growth trends.

Hypothesis 3: Protein and calorie intakes will be higher in cow's milk feedings than in formula feedings, and higher in formula feedings than in breast milk feedings.

Hypothesis 3 was designed to relate levels of intake during the first postnatal year to methods of feeding. If replacement of breast by formula feeding were indeed a factor in secular trends toward increased body size and accelerated growth (Stini, 1979a, 1981a), and if protein and

calorie intakes were prominent factors in modulation of growth rate, then infants fed exclusively by one method or the other should not only show appropriately altered growth (Hypothesis 2), but also appropriately altered intake of protein and calories.

Section Two: Nutrition, Growth, and Sexul Maturation

Hypothesis 1: Combined knowledge of growth and intake will better predict age of menarche than knowledge of growth or intake alone.

If resource allocation theorists are correct in characterizing growth and maturation as independent parameters of development, then dietary intake may have separate modulatory effects on each of these parameters. However, if growth and magturation are nondissociable parameters of development, then effects of diet on growth should carry over to maturation as well. In the latter case, knowledge of dietary intake should not improve growth-based predictions of menarcheal age, since effects of intake will already be subsumed within growth measurements. If, on the other hand, knowledge of diet improves growth-based predictions of menarcheal age, then dietary effects may not have been subsumed within growth measurements, and the possibility of separate dietary effects on separate developmental parameters will be preserved.

Hypothesis 2: Accelerated sexual maturation will be associated with greater protein and calorie intakes than delayed sexual maturation.

If dietary intake has direct modulatory effects on both growth and maturational processes, then relationships between protein/calorie intake and growth examined in Section One of the study may also be obervable in the case of protein/calorie intake and maturation. More specifically, accelerated maturation (operationally defined as early age of menarche) should be associated with increased protein/calorie intake, and delayed maturation (late arrival at menarche) with decreased intake of these dietary factors.

Section Three: Growth, Maturation, and Age-related Disease

Hypothesis: High energy expenditure across all major channels of resource allocation will be associated with greater incidence of later-life disease than low expenditure across these same channels.

If excessive energy expenditure throughout the lifespan is directly related to compromised health in later-life, then quantification of lifetime energy expenditure should make possible direct comparison between the incidence of disease in high-expending and low-expending individuals. The single hypothesis in Section Three asserted that individuals

with high cumulative energy expenditure would show greater incidence of age-related disease than their low-expending counterparts.

CHAPTER III

METHODS AND PROCEDURES

Survey Description

The Second National Health and Nutrition Examination Survey [NHANES II] was a cross-sectional survey conducted by the National Center for Health Statistics [NCHS] between February 20, 1976 and February 27, 1980. Data related to health and medical history, food consumption, and health-related behavior were collected through questionnaire response. Special clinical tests, laboratory analyses, and direct physical examination were also conducted. NHANES II was initially designed to obtain representative national data on the prevalence of disease and conditions of ill-health within the civilian noninstitutionalized U.S. population (United States Department of Health and Human Services, 1981a).

Sample Design

Data obtained by NHANES II was collected on a highly-stratified, multistage, probability cluster sample of households throughout the United States. A total of 27,801 persons from 64 sampling areas was selected as representative of the civilian, noninstitutionalized population of the United States. Subjects sampled ranged in

age from 6 months to 74 years. Certain subgroups in the population of special interest for nutritional assessment were deliberately oversampled. These groups included: preschool children ranging in age from 6 months to 5 years, persons 60 through 74 years old, and persons living in areas defined as poor by the United States Bureau of the Census for the 1970 Census. Actual sample selection was carried out by the United States Bureau of the Census according to NCHS specifications. A detailed description of the sample design for NHANES II has been previously published (United States Department of Health and Human Services, 1982).

Statistical Considerations in Secondary Analysis

Abraham (1986) has pointed out that the assumption of simple random sample is seldom appropriate for analysis of data obtained from a complex sample. Although point estimates can be accurately determined through weighted analyses which make use of individual case weights provided along with NHANES II data, estimates of variance must take into account design effects brought about by the complex sampling design of NHANES II.

Special computer programs have been developed for this purpose with the acknowledgment and support of the National Center for Health Statistics. One such program, entitled

"SURREGR", was used in the current analysis. This procedure was developed by Shah (1984) at the Research Triangle Institute in Research Triangle Park, North Carolina and embedded in the Statistical Analysis System [SAS]. The SURREGR procedure has been used previously in secondary analysis of NHANES II data (e.g., Pirkle, Schwartz, Landis & Harlan, 1985; Schwartz, Angle & Pitcher, 1986).

Exceedingly small subsample sizes in Section One and Section Three of the current study precluded use of the SURREGR procedure in analysis of these subsamples, since each contained an excessive number of primary sampling units [PSUs] with zero observations. Collapse of these "missing PSUs" into their observation-containing counterparts was viewed as an unacceptable violation of design assumptions in NHANES II. In Section Two and Section Four of the present study, SURREGR procedures were used to obtain variance estimates whenever subsample size allowed. In short, results of the present study are presented as weighted analyses only, except where specifically identified as SURREGR-based (i.e., design-sensitive) computations.

Nonresponse Bias in NHANES II

Rate of nonresponse during the examination phase of NHANES II has been estimated at approximately 27%

(Forthofer, 1983). Despite the magnitude of this factor, however, most statistically significant associations between inteview or examination status and variables in the survey appear to have been removed by post-survey adjustments performed at NCHS (Forthofer, 1983).

Acknowledgment of Assistance

The data and analyses used in this dissertation were made available through the Inter-university Consortium for Political and Social Research [ICPSR] in Ann Arbor, Michigan, and the National Technical Information Service [NTIS] of the U.S. Department of Commerce in Springfield, Virginia. Data for the Second National Health and Nutrition Examination Survey [NHANES II] were originally collected by the National Center for Health Statistics [NCHS] in Hyattsville, Maryland and the Bureau of the Census in Washington, D.C. Neither the collector of the original data, nor NTIS, nor the Consortium bear any responsibility for the analyses or interpretations presented herein.

General Principles of Subsample Selection

Four non-overlapping subsamples were selected for secondary data analysis. Principles of selection included (a) exposure to variables of interest (for example,

although total size of the NHANES II sample was 27,801 persons, only 20,322 completed dietary recalls); (b) conceptual relevance of age-related factors (for example, short-term effects of breast feeding on rate of growth could only be examined in subjects of proximate breast feeding age); (c) conceptual relevance of factors unrelated (or loosely related) to age (for example, the necessity of measuring reproductive lifespan in postmenopausal women); (d) implications of prior analyses (for example, the determination by Frisancho (1981) that maximum percentage increase in arm muscle area prior to adolescence occurred between the ages of 8 and 9 years in NHANES I subjects); and (e) practical considerations in rendering variables operational (for example, the lack of a quantifiable, maturational male counterpart to age of menarche in females).

Treatment of Gender

The difficulty in quantifying a reproductive parameter for NHANES II males prompted their exclusion from all subsamples in the study on which maturation-based hypotheses were to be tested. For the sake of consistency, exclusion of male subjects was then extended to all subsamples.

Treatment of Race

Previous investigations of growth, diet, and health in NHANES II have often avoided merger of black and white populations (e.g., Jones, Nesheim & Habicht, 1985; Koplan, Annest, Layde & Rubin, 1986; Schwartz et al., 1986;). This policy has resulted from repeated detection of large differences in dietary, anthropometric, and health-related measurements on blacks and whites. Large differences in protein and kilocalorie intake (NCHS, 1977), triceps skinfold measurement (Cronk & Roche, 1982), and calculated arm muscle area (Frisancho, 1982) have been previously reported for black versus white populations. Because each of these measurements had been designated as a variable of interest in the present study, subsampling in the study was restricted to white subjects.

Specific Steps in Subsample Selection

Section One: Nutrition and Growth

Subsample 1. Nutritional modulation of growth rate during the first postnatal year has frequently been ascribed to method of feeding (Bergmann & Bergmann, 1979; Butte & Garza, 1985; Fomon, 1986; Stini, 1979a, 1981a; Widdowson, 1986). Breast feeding has been associated with lower levels of protein and calorie intake than bottle-feeding of

commercial formulas or cow's milk (Fomon, 1986). In a comparison of NHANES II infants bottle-fed either cow's milk or commercial formula, Montalto, Benson & Martinez (1985) found significantly higher protein and calorie intakes in 7-12 month-olds fed cow's milk. Considered as a whole, these observations were interpreted as creating a methodological need for an age-related subsample of NHANES II infants in which level of nutrient intake could logically be ascribed to method of feeding.

Mean age for cessation of breast feeding in NHANES II infants has been estimated at 5.2 $\pm$ 5.2 months (ICPSR, 1984c). Such an estimate further implies that while 50% of all breastfed NHANES II infants continued to breast feed after their fifth postnatal month, less than 10% were still breastfeeding after their first postnatal year. Under these circumstances, it was considered methodologically inappropriate to try and ascribe differences in intake to method of feeding in infants older than 12 months. An upper age limit of 12 months was consequently set for the first subsample.

Mean age for introduction of solid foods to NHANES II infants has been estimated at 3.3 $\pm$ 3.6 months (ICPSR, 1984c). Because introduction of solid foods was expected to confound ascription of intake to method of feeding, elimination from the subsample of infants fed solid foods

was judged desirable. However, such elimination would have resulted in an unacceptably small subsample size. As an alternative to elimination of this confounding variable, a lower age limit of 6 months (coinciding with the earliest age of examination in NHANES II) was set on the subsample in an effort to help equallize the effect of the confound on growth variables of interest.

An age-related criterion of 6-12 months for Subsample 1 was further indicated by the finding of Frisancho (1974, 1981) that largest percentage increases in arm muscle area of NHANES I and II female infants occurred between the ages of 0.3-1.0 year. Given the impossibility of true growth measurement in any cross-sectional survey, maximization of growth-sensitive qualities in a static, anthropometric measurement was judged essential for eventual speculations about growth. It was reasoned that measurement of arm muscle area during a period of peak dynamic change would maximize its value as a potential growth indicator.

A final contributing factor in the selection of age limits for Subsample 1 was the finding by Montalto et al. (1985) that largest differences in protein intake for NHANES II infants fed cow's milk versus formula occurred between 7 and 8 months of age. An age-limited subsample containing

this time period was judged most likely to pick up on true differences in dietary intake.

Two screening variables were employed in selection of the subsample. When relatives of infants characterized the recall information provided about their infants as being either non-representative of the infant's usual way of eatin or ensuant to a recent dietary change, their infants were automatically excluded from the subsample. Screening of subjects in this manner was expected to help reduce the influence of intra-individual variability known to limit reliability of single-recall data (Balough, Kahn & Medalie, 1971; Bazzarre & Myers, 1979; Beaton et al., 1979).

Subsample 2. In clinical settings, cross-sectional growth standards have been judged inapplicable to children older than 9 years (Tanner & Davies, 1985). Beyond that age, individual variation in the timing of peak height velocity creates a fundamental discrepancy between the actual growth tempo of an individual and the growth standard (calculated difference between cross-sectional means) applied to him (Tanner & Davies, 1985).

While the present study was never intended to have specific clinical applications, the issue of individual growth tempo also helped dictate a younger-than-9 subsampling criterion in this research situation. Using NCHS

data which included subjects from NHANES I, Tanner & Davies (1985) determined a mean age for peak height velocity in females of 8.3 ± 0.9 years. (Subtraction of cross-sectional means computed by Frisancho (1981) for arm muscle area in NHANES I females revealed a similar peak during the eigth year.) Subsampling of NHANES II females at no later than 8 years of age was expected to maximize potential contrasts between females who had and had not attained peak height or arm muscle velocity.

Between 5 and 8 years of age, annual percentage increases in arm muscle area (Frisancho 1981), height and height velocity (Tanner, 1985), and sitting height (NCHS, 1981) have been shown to be relatively constant for females in the United States. Below the age of 5, however, height velocity in females is known to be significantly higher (Tanner, 1985). Since increases in growth velocity known to be associated with the natural history of growth might be expected to obscure other increases associated with enhanced dietary intake, a lower age limit of 5 years was placed on subject entry into Subsample 2.

Section Two: Nutrition, Growth, and Sexual Maturation

Subsample 3. The character of human growth and maturation as genetically "targeted" phenomena (Tanner,

1979) served as a starting point for consideration of selection criteria for Subsample 3. Concern with genetic targeting centered on its potential for "cancelling out" the effects of nutrition on growth rate. From a research point of view, genetic influences have proven so extensive that investigators have found it necessary to prepare parent-related age-growth standards in order to successfully predict growth (Garn and Rohmann, 1966).

In this study, the problem of genetic targeting translated into a problem of circumventing "catch-up" and "catch-down" growth. Given time, nutritionally-stunted individuals could be expected to "catch up" (at least in part) to their genetically-targeted statural endpoints, and conversely, nutritionally-accelerated individuals could be expected to do some "catching down". Nutritional factors could not be expected to account for much variation in anthropometric measurements if those measurements were taken after periods of "catch up" and "catch-down" growth. At the same time, relationships between growth and maturation could not be accurately addressed if compensatory periods of growth were altogether excluded from analysis.

A decision to set 18 years of age as the upper limit on subsample selection was based on the observation by Frisch &

Revelle (1970) that "catch-up" growth in women nears completion at that time. Descriptive statistics developed on a subsample extended in age to 18 years was expected to reflect contributions of compensatory growth to statural development. At the same time, hypothesis testing which involved prediction about growth and maturation was carried out on a limited segment of this subsample ranging in age from 11-15 years. (Rationale for selection of these particular and narrowed age boundaries are been presented later in this chapter under the heading "Variable Selection in Secondary Analysis"). Analysis of subjects from this narrower age range was expected to help reduce the influence of compensatory growth on dependent variables and increase the probability for detection of nutritional influence.

Two further screening techniques were used in selection of subjects for Subsample 3. The first involved circumstance-of-recall factors and has been described previously. The second involved length of time between age of menarche and date of recall. Because an overriding purpose of the study was to obtain information about the effect of intake upon rate of growth and maturation, information about nutrient intake which applied only to postmenarcheal eating habits was considered inappropriate for analysis. At the same time, the cross-sectional nature

of the survey meant that recall data and knowledge of menarche had to be obtained simultaneously, or, expressed somewhat differently, that information about dietary intake prior to menarche could not be directly obtained for any subject. In order to avoid exaggerating this "ex post facto" character of recall data, subjects for whom recall data postdated age of menarche by a minimum critical time period were eliminated from the subsample. This minimum critical time period was calculated by taking the [mean - standard deviation] level of the dependent variable (age of menarche) and subtracting the resulting value from 12 years of age (the youngest age in NHANES II to self-report reproductive history).

Section Three: Growth, Maturation, and Age-related Disease

Subsample 4. Analysis of age-related, epidemiological trends in disease-related variables served as the basis for establishment of age limits on Subsample 4. The two disease-related variables chosen for this section of analysis were osteoporosis and malignant neoplasms.

Subsample 4 and osteoporosis. Diminution of compact bone in U.S. females has been estimated to begin around 40-45 years of age (Mazess, 1982). When defined as the ratio

of metacarpal cortical area to total metacarpal area, osteoporosis has been estimated to undergo its period of greatest increase around 48 years of age (Wright, 1983). Post-mortem estimates of skeletal density in white females also point to the fourth decade of life as the period for onset of greatest density losses (Trotter & Hixon, 1974). The incidence of hip fractures among white females in the U.S is known to double between the age brackets of 50-59 versus 60-69 years (Cummings, Kelsey, Nevitt & O'Dowd, 1985), and osteoporosis has been shown to be an important underlying cause of hip fractures (Melton, Wahner, Richelson, O'Fallon & Riggs, 1986).

Subsample 4 and malignant neoplasms. The incidence of breast cancer among white females in the United States has been shown to increase by approximately 100% between the age brackets of 40-44 and 50-54 years (Schottenfeld & Fraumeni, 1982). A 79% increase in rate of death from malignant neoplasms of the breast in white females has been also been reported between the age brackets of 45-54 and 55-64 years (United States Department of Health and Human Services, [USDHHS], 1986).

Age limits on subsample 4. Increases in the incidence of any disease which are known to be associated with its

natural history might be expected to obscure any "unnatural" increases associated with growth acceleration or increased cumulative energy expenditure. Measurement of subjects at a point in time prior to the occurrence of such "natural" increases was therefore regarded as a desirable step in the selection of Subsample 4. Consideration of the epidemiological findings cited above prompted establishment of an upper age limit of 55 years for this subsample.

A lower age limit of 50 years was arrived out through a similar series of considerations involving increased incidence of disease between the age brackets of 35-44 and 45-54 years. Estimated percentage increases in the incidence of the above-mentioned diseases have been found to be equally (and sometimes even more) dramatic between these earlier age brackets (Haynes & Feinleib, 1980; Schottenfeld & Fraumeni, 1982; USDHHS, 1986); but as these ages drop lower and lower, so does the absolute incidence of disease, and the probabilities for occurrence turn out to be exceedingly small. For example, probability of breast cancer in 30-34 year-old white females in the United States has been estimated at 1:4000 (Schottenfeld & Fraumeni, 1982). The "mid-life" character of this 35-44 year-old age bracket and the small probability of disease occurrence associated with it make age-related interpretations of disease highly

questionable in this context. Given this difficulty, a lower age limit of at least 44 years seemed appropriate for Subsample 4.

Establishment of the lower age criterion for Subsample 4 was further based upon analysis of menopausal age in U.S. women. Estimates of central tendency for menopausal age have been noted for their remarkable consistency both cross-culturally and over time (Cutler & Garcia, 1984; Wu, 1985). An estimated mean menopausal age at 50 $\pm$ 1.5 years has been suggested by Cutler & Garcia (1984) as being most representative of worldwide epidemiological findings. Numerous studies carried out exclusively on samples of United States women lend general support to this contention (Goodman, Grove & Gilbert, 1978; McKinlay, Bifano & McKinlay, 1985; Treloar, 1981).

The age criterion of 44 years suggested by epidemiological analysis of disease seemed too low when examined in the context of these menopausal estimates. Using the mean and standard deviation estimates suggested by Cutler & Garcia (1984), an age of 44 would stand 4.0 standard deviations below the mean, indicating that less than one percent of all women would be expected to reach menopause by this age. Even using the largest estimate of

variability associated with a point estimate for menopausal age -- a standard deviation of 4.37 years reported by Goodman et al. (1978) established on a sample of Caucasian women living in Hawaii) -- the age of 44 years would remain 1.39 standard deviations below the mean and would indicate that less than 9% of the target population could be expected to reach menopause by age 44. Inclusion of women in Subsample 4 from an age bracket in which the occurence of menopause remained extremely unlikely was regarded as undesirable, since factors responsible for this unusually early occurrence of menopause were expected to confound relationships of interest. On the basis of these expectations, and in keeping with the central tendency of menopausal age, a lower age limit of 50 years was established for Subsample 4.

Variable Selection in Secondary Analysis

Recumbent Length/Standing Height

Subsample 1. Numerous studies of infant growth and nutrition, including studies on NHANES II infants, have chosen recumbent length as a dependent variable of key importance (Bergmann & Bergmann, 1979; Butte & Garza, 1985; Garn & Rohmann, 1966; Jones et al., 1985; Schelpo, Pongpaew, Vudhivai & Sornmani, 1986). Recumbent length has been used by Brooke (1986) in determination of energy needs

during infancy, and by Fomon (1986) in assessment of infant protein requirements.

Although Zeras (1979) has referred to height/length as the traditional standby for field measurement of skeletal growth, Malcolm (1986) has argued that because growth in height variation within populations correlates with number of teeth erupted, growth in height is very likely to be a measurement under strong genetic influence and almost completely resistent to environmental/nutritional factors.

In spite of Malcolm's argument, the secular trend for infant length -- presumably containing a nutritional component -- has been estimated to include a 2.8 centimeter increase for 1-year-old males between 1865 and 1962 (Meredith, 1963). A similar increase for recumbent length has also been reported by Roche (1979).

With the exception of a brief period of time commonly referred to as the adolescent "growth spurt", annual increments in height are known to diminish from birth onward (Lowrey, 1986), and the greatest percentage increase in recumbent length/height is known to occur during the first postnatal year. Given this peak possibility for change, the chance for nutritional modulation of growth to be reflected in recumbent length/height was judged to be maximal during the first postnatal year. This observation "tipped the

evidentiary scale" in favor of inclusion of recumbent length in analysis of 6-12 month-olds.

Subsample 2. In his calculation of clinical longitudinal height and height velocity standards for North American children, Tanner (1985) has estimated mean peak height velocity in women to occur at 8.3 ± 0.9 years. In the event of growth acceleration, this point estimate would be expected to drop down into the 5-8 year-old age range established for subsampling in this research area. As a consequence, standing heights attained by 5-8 year-old subjects should be increased. In the absence of growth acceleration, or in the presence of growth delay, estimates at or above the mean would once again be expected to apply, and as a result, peak height velocity would occur after the 5-8 year-old age range. In this case, standing heights attained by 5-8 year-olds should be average at best.

Like recumbent length, the measurement of height has been consistently associated with a trend toward secular increase (Falkner & Tanner, 1979; Himes, 1979; Lowrey, 1986; Malina, 1979; Matsumoto, 1982; Meredith, 1963, 1976; Micozzi, 1985; Roche, 1979; Stini, 1979a, 1981a; Tanner, 1962, 1968; Weir, 1952). In explanation of this secular trend, most researchers have acknowledged the possibility of

a nutritional component. The potential for height to reflect nutrient-mediated changes in body size at the epidemiological level further encouraged its inclusion in the present study.

Subsample 3. Research interest has repeatedly focused on standing height as an indicator of growth during adolescence (Dreizen et al., 1967; Richey, 1937; Shuttleworth, 1937, 1938, 1939; Tanner, 1968, 1986). The finding that peak height velocity immediately precedes onset of menarche (Billewicz et al., 1976; Frisch, 1974, 1978, 1983; Frisch & Revelle, 1970; McNeill, 1963) has also sparked interest in this anthropometric measurement.

Mean percentage increases in standing height between ages 12 and 15 in NHANES I females are known to range from 1-3% (Frisancho, 1981). From this standpoint, the opportunity for nutritional modulation of growth to be reflected in height measurements during this time period appears quite limited. However, prior success with height measurements in longitudinal data (Dreizen et al., 1967) and interpretative advantages stemming from availability of height standards applicable to NHANES II females prompted inclusion of standing height in this area of research.

Arm Muscle Area

Subsample 1. As an indirect indicator of protein reserves, muscle mass has traditionally been used to assess nutritional status during infancy and childhood (Frisancho, 1974). The assumption that a greater muscle size represents a greater protein reserve has been endorsed by Frisancho (1974). The ability of arm muscle area to reflect nutritional modulation of growth as early as six months of age has been experimentally demonstrated by Mills et al. (1986).

Data compiled by Frisancho (1981) on female infants in NHANES I has shown peak changes in arm muscle area to occur between 0.3 and 1.0 years of age. During this period, percentage increases are three times higher than during any comparable time period. The opportunity for nutritional modulation of growth to be reflected in arm muscle area measurements was judged to be maximal during this 4-12 month time period.

Particular sensitivity of arm muscle area to protein and kilocalorie (versus fat and carbohydrate) intake (Frisancho, 1974), superiority of muscle area to skinfold thickness as a nutritional indicator in populations with normal degrees of fatness (Kreiger, 1982), and superiority of areas to circumferences (Gurney & Jelliffe, 1973) were

further reasons for use of arm muscle area as an early-life growth indicator. Actual calculation of arm muscle area was based on right triceps skinfold and right upper arm girth measurements as inserted into the formula originally developed by Gurney (1969) and used by Frisancho (1981) in development of arm muscle norms from NHANES I data.

Subsample 2. Analysis of NHANES I data by Frisancho (1981) has indicated a pre-adolescent "jump" in the arm muscle area of females during the 8.0-8.9 year-old age bracket. In the case of growth acceleration, this spurt would be expected to show up even earlier. Measurement of arm muscle area in 5-8 year-old females was expected to maximize the opportunity for detection of growth acceleration in this age group.

Subsample 3. Mills et al. (1986) have argued that although standing height, triceps skinfold thickness, and arm muscle mass are all correlated, arm muscle mass is the strongest predictor of pubescence. Their success in associating infant arm muscle areas with progression of puberty in a longitudinal study of 78 males, together with the known sensitivity of arm muscle area to protein and calorie nutrition (Kreiger, 1982; Frisancho, 1974) were the

key factors which lead to incorporation of arm muscle area into this section of the study.

Absolute Protein, Carbohydrate, Fat, and Calorie Intake

Subsamples 1, 2, and 3. The problem of intra-individual variability (the variation of an individual around his true mean) in dietary research is known to be particularly acute when single 24-hour recalls are used in dietary analysis (Beaton et al., 1979; Beaton et al., 1983). The accuracy of correlation coefficients can be seriously compromised by high intra-individual variability (Liu et al., 1978), as can the power to detect specific between-group differences (McGee et al., 1982).

Conversion of absolute intake data (e.g., grams of protein) into some scaled form (e.g., grams of protein per 1000 calories) has been recommended by Beaton et al. (1983, 1979) as one way of reducing the high intra-individual variability typically associated with single recall data. Two considerations led to the rejection of such a step in the present analysis. First was the finding of Butte & Garza (1985) that conversion of absolute to scaled data did not help account for variability in growth rate attributable to protein intake during the first postnatal year. Second was

the observation by Beaton et al. (1979, 1983) that conversion of absolute to scaled data had its maximal impact when gender effects were most prominent. Since males had been excluded from the present study, no such effects were possible.

Sitting Height/Standing Height Ratio

Subsample 2. Differential growth rates for various linear segments of the body are known to be useful in evaluating nutritional effects on early growth (Haas & Flegal, 1981; Tanner, 1962). Leg growth, for example, is known to lag behind trunkal growth during the fifth prenatal month, but to increase gradually from the sixth postnatal month onward, and ultimately undergo dramatic acceleration during acquisition of upright posture (Lowrey, 1986).

The carefully-timed interplay of trunkal and lower extremity growth is known to produce a distinct developmental pattern in sitting-to-standing height ratio. At birth, this ratio approaches .85:1, and gradually diminishes until the age of 10, at which time a level of .5:1 is reached (Lowrey, 1986; Vital and Health Statistics, 1981). This observation is supported analysis of data from the University of Iowa Studies in Child Welfare (Baldwin, 1921) and by examination of NHANES I data (NCHS, 1981). In

NHANES I data, percentage decline in this ratio is approximately 15% between the ages of 1-5 as well as between the ages of 5-10. It should be noted, however, that in the NHANES I data, the overall decline in sitting-to-standing height ratio is somewhat less than predicted, "bottoming out" at .53:1 instead of .5:1 around 10 years of age.

The uniqueness of 10 years as an developmental endpoint in the anthropometry of sitting-to-standing height ratios encouraged inclusion of this measure in analysis of 5-8 year-olds in Subsample 2. A further consideration in selection of sitting-to-standing height ratio was the secular trend associated with it. Pre-pubescent decreases in this ratio have been described by several researchers (Hamill, Johnston & Lemeshow, 1973; Himes, 1979; Malina et al., 1973). Himes (1979) has speculated that since relative decreases in sitting height are known to accompany normal growth, this secular trend toward lower ratios may simply be reflective of accelerated growth. Because ability to reflect alterations in growth rate was a criterion for selection of dependent variables in this area of research, Himes' speculation was considered as further evidence for inclusion of this variable in the study.

Circumstances of extreme disproportionality (i.e., unusually short legs and long trunks producing falsely

elevated sitting-to-standing height ratios, and vice-versa) were known to act as potential confounds in this section of the study. Failure to control for such circumstances was therefore recognized as a limitation on analysis of data involving sitting height:standing height ratios.

Age of Menarche

Subsample 3. Age of menarche has been used extensively in studies of human maturation and its etiological components (Dreizen et al., 1967; Frisch, 1974; Frisch & Revelle, 1970; Malina, 1979; Roche, 1979; Shuttleworth, 1937, 1938; Zacharias et al., 1970). In addition secular trend in age of menarche has been a topic of widespread interest and debate (Bullough, 1981; Burger & Gochfeld, 1985; Danker-Hopfe, 1986; Golub, 1983; Frisch, 1978; Jafarey et al., 1970; Lowrey, 1986; Malina, 1979; Stini, 1979a, 1981a; Tanner, 1968, 1986). Despite differences of opinion as to the magnitude, etiology, and duration of the change, however, researchers have agreed upon the existence of a secular trend toward decreased age at menarche. Responsiveness of this variable to changing environmental conditions has also lent support to the possibility that age of menarche might show sensitivity to nutrition- and growth-related factors in this study of NHANES II females.

More specific physiological meaures (e.g., serum LH, FSH, progesterone or estradiol patterns) would clearly have been preferable as indicators of maturational status in the present study, particularly since such measures have recently been tested in animal-model research (Glass et al., 1979; Holehan & Merry, 1985; Merry & Holehan, 1979), However, self-report data on age of menarche proved to be the only direct indicator of sexual maturity contained in NHANES II data.

Age-related Disease: General Considerations

The list of chronic, degenerative diseases known to be associated with the natural history of aging is both controversial and extensive. Part of this controversy stems from conceptual confusion about the relationship between aging and health (Johnson, 1985; Weindruch et al., 1979). Another part is related to difficulty in identification of disease patterns unique to aging given the knowledge that all homeostatic systems in the body undergo progressive loss of effectiveness with increasing age.

Kohn (1985) has argued that relationships between aging and disease can be broken down into three fundamental categories. The first category includes all diseases considered to be inevitable components of aging and

experienced by all humans at least to some degree (e.g., atherosclerosis, osteoporosis). Second are those diseases which are not part of the normal aging but which are subject to large increases in incidence during the latter stages of life (e.g., malignant neoplasms, hypertension). In the third category are those diseases which are neither part of normal aging nor subject to particular age-related increase, but which are simply more likely to cause death in elderly populations (e.g., accidents, respiratory infection).

Recent reviews of age-related disease have tended to include diseases from all three of Kohn's categories. For Dilman (1981), the overall list includes maturity-onset diabetes, atherosclerosis, essential hypertension, mental depression, metabolic immunodepression, autoimmune disease, and cancer susceptibility. A recent anthology edited by Young (1986) has focused on these same basic seven, with the notable addition of osteoporosis. Lists compiled by Besdine (1982), Blumenthal (1983), and Brody & Brock (1985) have included similar (although more extensive) entries.

Three criteria were used for selection of age-related diseases in the present study: (a) appearance of the disease on a majority of the above-mentioned lists; (b)

possession by the disease of a protein-related etiological component; and (c) potential for association of the disease and its occurrence with alterations in rate of growth or maturation. While a number of diseases were determined to satisfy two of these three criteria listed , only two were determined to satisfy all three. These two diseases were osteoporosis and malignant neoplasms. Evidence used in making this determination is presented below.

Osteoporosis. The possibility of a protein-related component in the etiology osteoporosis was suggested by two sets of research findings. The first set of findings focused on the phenomenon of protein-induced hypercalcuria (Allen, Oddoye & Margen, 1979; Margen, Chu, Kaufmann & Calloway, 1974; Rekha & Linkswiler, 1974). Creation of negative calcium balance by means of chronic high protein intake has been offered by these researchers as a possible mechanism in the development of osteoporosis.

The second set of findings, summarized by Wachman and Bernstein (1968), postulated an increased demand for phosphate buffer (stored in bone) in the presence of acid loads (created by high protein intake). Life-long utilization of this phosphate-buffering capacity of bone was proposed as a key component in the etiology of osteoporosis.

Evidence suggesting a link between osteoporosis and

rate of growth or maturation has remained more tenative and complex, and has hinged upon the existence of post-maturational deficits in calcium intake. Linear bone growth is known to cease following calcification of epiphyseal plates and fusion of epiphyses with diaphyses (Lowrey, 1986). The proximal epiphyses of the tibia and fibula are among the last to close, and this event is known to currently take place in U.S. females between 17 and 19 years of age (Lowrey, 1986). Cessation of linear bone growth shortly after attainment of sexual maturity does not bring an end to total bone growth, however. Mineralization of the protein matrix is known to continue on into the fourth decade of life, at which time peak bone mass and density are finally reached (Lowrey, 1986).

Based on analysis of NHANES II data by Carroll et al. (1983), median calcium intake for U.S. females has been determined to drop below the RDA around 11 years of age, and to continue dropping very slightly throughout the remainder of life (Heaney, 1986). Considered within this context, acceleration of growth rate might make healthy bone development more difficult by increasing the imbalance between quantity of bone needing mineralization and quantity of calcium available to do it.

Under normal growth conditions, calcium deficiencies might affect development of bone length as well as density, leaving less bone to mineralize and less calcium for the task. But since it would allow a greater percentage of linear bone growth to be completed before the onset of calcium deficiency, while simultaneously leaving bone mineralization to suffer the full effects of that deficiency, growth acceleration might be a factor increasing the risk of osteoporosis. Although not analyzed within the context of growth rate, post-maturational calcium deficiencies have previously been shown to promote osteoporosis in cats and other mammals (Heaney, 1986).

Malignant Neoplasms. Although the role of protein intake in the development of malignant carcinomas has been less clearly defined than the role of total caloric or fat intake, evidence for a protein component has emerged from a wide range of research findings. Experimentation with rats by Ross and Bras (1965) showed increased risk for certain (but not all) types of malignancy given increased protein intake under conditions of caloric constancy. Later research by Ross (1977) indicated decreased tumorigenesis under conditions of low protein intake. A more recent case-control study by Heshmat et al. (1985) has demonstrated

an epidemiological relationship between increased protein intake and incidence of prostate cancer in human males.

Micozzi (1985) has reviewed ten years of positive findings in epidemiology with respect to the role of high protein intake in the development of breast cancer. Results in this area have been somewhat confounded, however, by particularly strong results associated with consumption of animal versus total protein, thus inviting the possibility of a fat-related effect in carcinogenesis.

The association of carcinomas with rate of growth and maturation has been established most convincingly in the area of breast cancer research. The role of menearcheal age in the development of breast cancer has been a topic of long-term epidemiological interest (Micozzi, 1985; Sherman, Wallace, Bean & Schlabaugh, 1981; Staszewski, 1971, 1977). Increased risk of breast cancer associated with early onset of menarche has been difficult to separate, however, from alteration in growth parameters closely associated with attainment of menarche. Body size and body mass indicators (e.g., standing height, body surface area) have been shown to reflect risk of breast cancer in several epidemiological studies (de Waard, 1975; Kelsey, 1979; Sherman et al., 1981; Staszewski, 1977). Willett (1987) has indicated that stunt-

ing of childhood growth in females might succeed in reducing the incidence of breast cancer. Considered as a whole, these various studies were viewing as confirming a potential link between the development of malignant neoplasms and rate of growth or maturation.

Age-related Disease: Specific Considerations

Questionnaire-derived data in the NHANES II medical history included information related to history of chronic and acute disease, history of medical diagnosis, and hisory of recent hospitalization. Among these three sources for dependent variables, only history of recent hospitalization offered variables particular to osteoporosis and malignant neoplasms. Even here, there were limitations. Hospitalization for malignant neoplasms had been coded as such. However, the hospitalization coding most directly related to osteoporosis was "Fractures or Dislocation (current)". Because osteoporosis has been shown to be an important underlying cause of fractures in later life (Melton et al., 1986), and because 25% of all white females in the United States are estimated to experience one or more fractures by age 65 due to osteoporosis (Phillips & Gaylord, 1985), hospitalization for fracture was accepted as a surrogate indicator of osteoporosis. Fracture unrelated to

osteoporosis remained a confound in this section of the analysis.

History of recent hospitalization as collected in NHANES II included information on as many as three hospitalizations. Because sample size associated with second and third hospitalizations was extremely small, however, information related to the first instance of hospitalization was used exclusively in this section of the analysis.

Cumulative Energy Expenditure

Three broadly-defined channels for energy expenditure have been ascribed to living organisms. Energy resources can be allocated to cover metabolic costs associated with growth, reproduction , or body maintenance (Brooks & Wiley, 1986; Calder, 1985; Pianka, 1981). This three-fold analysis of energy allocation has been applied to the ecological behavior of a variety of organisms, including plants, trees,and mammals, including man (Bronson, 1985; Edlin, 1976; Millar & Zammuto, 1983; Pianka, 1981; Roff, 1986). Within this three-fold classification system, the category of "maintenance" is assumed to include metabolic costs associated with body size, traditionally approximated by a combination of measurements representing linearity and mass (Peters, 1983; Roff, 1986; Schmidt-Nielson, 1984).

Application of this conceptual framework to growth, reproductive, and maintenance costs of NHANES II subjects resulted in the selection of 5 variables for statistical analysis. Two of these variables were required for assessment of maintenance costs: standing height and weight$^{3/4}$. Reproductive costs were represented by length of reproductive lifespan, i.e., length of time between age of menarche and age of menopause, and by total number of live births. Age of menarche was chosen as a surrogate measure to represent metabolic costs associated with growth.

Representation of maintenance costs. Linear and mass aspects of body size were represented by standing height and weight$^{3/4}$, respectively. Standing height was chosen as the best indicator of linearity despite known limitations on its use with elderly subjects brought about by kyphosis and shortening of the spinal column with age (Mitchell & Lipschitz, 1982). The relative youthfulness of Subsample 4 subjects in comparison with subjects evaluated in studies of kyphosis and spinal column shortening, and previous inclusion of height in assessment of energy expenditure were further considerations in selection of height as a measurement of linearity. Weight$^{3/4}$, previously identified as the best representation of metabolic body size in mammals

(Kleiber, 1947; Pike & Brown, 1984), was selected to represent body mass.

Representation of growth costs. Limitations on assessment of growth superimposed by the use of cross-sectional data were felt most acutely in this area of research. Selection of age of menarche to represent growth-directed energy expenditure was based upon successful use of this variable by Frisch (1974) in assessing rate of growth, and upon the assumption that accelerated growth would be reflected in early menarcheal age (and vice-versa). Failure to account for non-growth components of menarcheal age was considered as an important limitation on the use of menarcheal age in this context.

Representation of Reproductive Costs. Number of offspring and length of reproductive lifespan have traditionally been cited as key components in the assessment of reproductive costs (Austin & Short, 1982; Bronson, 1985; Calow, 1979; May & Rubenstein, 1982; Sadleir, 1969). Simple subtraction of menarcheal age from menopausal age as self-reported by NHANES II subjects was the procedure used to quantify reproductive lifespan in this section of the analysis. In the absence of detailed knowledge about circumstances surrounding miscarriage and abortion for

subjects in Subsample 4, number of offspring was equated with number of self-reported live births. Increase in reproductive costs associated with unsuccessful pregnancy were not considered in the analysis and were considered as potential confounds in assessment of results.

Statistical Procedures and Hypothesis Testing

In general, a two-step procedure was used in hypothesis testing. Examined final weights provided by NCHS along with NHANES II data were used as sampling weights in the preliminary stage of the analysis to determine all point estimates. Design effects associated with the sampling design of NHANES II were ignored during this initial stage. As a second step, whenever subsample size allowed, adjustment was made not only for sampling weights but also for design effects through use of a SAS "SURRERG" procedure described earlier (Shah, 1984).

Subsample 1

A multiple regression of intake variables on recumbent length was carried out to determine effects of individual nutrient and kilocalorie intake on growth. Regression coefficients were considered as partial regression coefficients and were evaluated by examination of statistics associated with SAS Type III sums of squares (SAS

Institute, 1985). A separate multiple regression of intake variables on arm muscle area was carried out and handled identically.

Descriptive statistics for recumbent length and arm muscle area were computed on a month-by-month basis (e.g., mean arm muscle area for all 6-month-olds, for all 7-month-olds, etc.). Subjects scoring at least one standard deviation above their age-appropriate monthly mean on each dependent variables were assigned to a group labeled "Growth Delayed". Those infants scoring at least one standard deviation below their age-appropriate monthly means were assigned to a group labeled "Growth Accelerated". Unassigned subjects dropped out of the analysis at this point. A t-test procedure was used to determine the presence of significant mean differences in intake between the two groups.

A categorical dependent variable called "Method-of-Feeding" was created for the final stage of analysis on this subsample. The three levels of this dependent variable ("Breast-fed", "Formula-fed", and "Fed Cow's Milk") were constructed in such a way that subjects receiving mixed feedings were eliminated from the analysis. A Tukey means comparison option available within the GLM procedure in SAS (SAS Institute Inc., 1985) was used to

assess between-group differences in caloric and protein intake.

Subsample 2

Although dependent variables of interest in this section of the study were standing height, sitting-to-standing height ratio, and arm muscle area, statistical procedures used in analysis of Subsample 2 were identical to those previously described for analysis of Subsample 1. The presence of three dependent variables in this section of the analysis was handled through the use of three separate regression analyses. No Method-of-Feeding variable was created for this section of the study.

Subsample 3

Mean age of menarche for all white females 18 years or younger was computed and then used to divide subjects into two maturational groups. A categorical variable labeled "Rate of Maturation" was then created based on subjects' menarcheal ages. Subjects whose menarcheal ages were at least one standard deviation above the mean were assigned to a group labeled "Delayed Maturation". If a subject's menarcheal age was at least one standard deviation below the mean, she was assigned to a group labeled "Accelerated Maturation". Unassigned subjects dropped out of the

analysis at this point. "Accelerated" and "Delayed" groups were further screened for appropriateness of recall and menarche-recall time lag as previously described.

In order to test the first hypothesis (that combined knowledge of growth and intake would be a better predictor of menarcheal age than knowledge of growth or intake alone), a MAXR procedure (SAS Institute Inc., 1985) was used in conjunction with a model regressing intake and growth variables on menarcheal age. In order to test the second hypothesis that accelerated maturation would be associated with higher protein and calorie intake than delayed maturation, a t-test was used to determine the presence or absence of significant differences in mean intake between maturational groups.

Subsample 4

Means for all independent variables in this section of the study were computed on an annual basis (e.g., mean length of reproductive lifespan for all 50 year-olds, mean length for all 51 year-olds, etc.). Subjects scoring at least one standard deviation above their age-appropriate mean on each independent measure were assigned to a group labeled "High Energy Expenditure". Subjects scoring at least one standard deviation below their age-appropriate means

were assigned to a second group labeled "Low Energy Expenditure". Unassigned subjects were eliminated from further analysis.

Given the presence of categorical independent and dependent variables in this section of the analysis (e.g., hospitalization for cancer = "yes" or "no", energy expenditure = "high" or "low"), a chi-square procedure was used to test the hypothesis of greater disease incidence in the "high" versus "low" expenditure group. The null hypothesis in the chi-square analysis asserted independence of hospitalization-for-disease from level of energy expenditure.

CHAPTER IV

RESULTS AND DISCUSSION

Results of statistical testing on eight research hypotheses are presented in this section of the study. A general framework for presentation of results is outlined in Table 1.

TABLE 1

Framework for Presentation of Results

Theme of Section	Subsample Description	Number of Hypotheses
NUTRITION AND GROWTH	6-12 month-old white females (Subsample 1)	3
	5-8 year-old white females (Subsample 2)	2
NUTRITION, GROWTH, AND SEXUAL MATURATION	11-15 year-old post-menarcheal white females (Subsample 3)	2
GROWTH, MATURATION, AND AGE-RELATED DISEASE	50-55 year-old post-menopausal white females (Subsample 4)	1

One overriding limitation in all analyses was the dramatic reduction in subsample size which occurred as a consequence of age, race, sex, reproductive and recall

restrictions being placed on subject entry into subsamples. Numerical effects of subject screening are summarized in Table 2.

TABLE 2

Effects of Subject Screening on Subsample Size

Screening Variable	Subsample 1 (n)[a]	Subsample 2 (n)	Subsample 3 (n)	Subsample 4 (n)
Age and sex[b]	164	693	3,603	405
Reproductive status[c]	NA[d]	NA	779[e]	316
Race	145	536	622	265
Recall content[f]	45	276	183	NA
Recall recency[g]	NA	NA	46	NA
Final size	45	276	46	265

[a] Number in subsample.
[b] Initial subsample size based on selection of females of pre-determined age with no missing data for variables of interest.
[c] Post-menarcheal for all subjects admitted to Subsample 3 and post-menopausal for all subjects admitted to Subsample 4. Subsample 4.
[d] Not applicable.
[e] Effects of screening variables are presented cumulatively from top to bottom of table, e.g., number of age-appropriate females with no missing data in Subsample 3 equals "3,603", while number of age-appropriate females with no missing data values and post-menarcheal status equals "779".
[f] Subjects for whom dietary recalls were described as either (a) non-representative of usual eating patterns or (b) subsequent to a recent dietary change were excluded from Subsamples 1, 2, and 3.
[g] Subjects were excluded from Subsample 3 if the time interval between menarche and recall procurement was greater than one year.

Section One: Nutrition and Growth

Subsample 1: Descriptive Data

Independent variables. Subjects were unequally distributed across the seven-month age-range, with over twice as many subjects (28/45, or 62%) in the upper versus lower (12/45, or 27%) three-month interval. Caloric intake remained fairly steady from six to twelve months (1054.64 ± 50.51 calories (X ± SE, where X = mean and SE = standard error) for all months combined, with the exception of markedly low intake (792.08 ± 90.97 calories) at the seven-month level. A similar pattern was observed for mean protein intake, with six out of seven monthly means differing in magnitude from the overall mean (41.56 ± 2.63 grams) by less than ten percent.

When recall content was eliminated as a screening variable for 6-12 month-old subjects, increasing subsample size from 45 to 145, the overall means for protein and caloric intake were each reduced by approximately six percent. Although monthly deviations from the overall caloric mean remained small and never exceeded a magnitude of 15%, monthly protein intake showed a small but increasing trend not observed in the recall-restricted sample. At six, seven, and eight months of age, mean protein intake fell at least 13% below the overall mean; at nine months of age,

right on it; and at ten and twelve months of age, at least 11% above it. Actual values are presented in their entirety in the Appendix.

Protein and calorie estimates derived from fully-restricted (n = 45) and expanded subsamples (n = 145) were generally consistent with previous findings from the full cohort of NHANES II female infants ages 6-11 months. Carroll et al. (1983) estimated protein intake for this group at 40 ± 1.54 grams, and caloric intake at 991 ± 25 calories.

At each monthly interval, mean protein intake was at least 200% of the 1980 recommended dietary allowance (RDA). As a percentage of the RDA, mean caloric intake ranged from 98%-143%. Table 3 pinpoints exact RDA comparisons and specifies assumptions involved in their computation.

Dependent variables. In both fully-restricted and expanded subsamples, mean anthropometric measurements tended to increase with increasing age (Table 4). All estimates were in general agreement with previously reported 50th percentile values for NHANES II female infants and similarly surveyed groups (Lowrey, 1986; Hamill, Drizd, and Johnson, 1976; Frisancho, 1974).

TABLE 3

Percentage RDA Intake by Nutrient and Age of Subject

AGE[a]	WEIGHT[b] (kg)	PROTEIN RDA[c] (g)	CALORIE RDA[d]	% PROTEIN	% CALORIES
6	7.2	14.4	756	202	143
7	7.7	15.4	809	251	98
8	8.2	16.4	861	279	139
9	8.6	17.2	903	270	123
10	8.9	17.8	935	262	125
11	9.2	18.4	966	202	106
12	9.5	19.0	998	222	105

[a] Age in months.
[b] Monthly weight estimates based on 50th percentile values computed by the National Center for Health Statistics and published as the *1977 Ross NCHS Percentile Growth Charts* (American Dietetic Association, 1981).
[c] Estimated body weight multiplied by the recommended dietary allowance of 2.0g per kg of body weight for 0.5-1.0 year-olds (National Academy of Sciences, 1980).
[d] Estimated body weight multiplied by the recommended energy intake of 105 kilocalories per kg body weight for 0.5-1.0 year-olds (National Acedemy of Sciences, 1980).

TABLE 4

Monthly Means for Recumbent Length and Arm Muscle Area

AGE (months)	RECUMBENT LENGTH (cm) (n = 45)	RECUMBENT LENGTH (cm) (n = 145)	ARM MUSCLE AREA (mm^2) (n = 45)	ARM MUSCLE AREA (mm^2) (n = 145)
6	68.98 ± 1.41[a]	67.04 ± 2.21	895.08 ± 125.80	927.56 ± 87.66
7	65.91 ± 1.51	65.55 ± 0.65	771.28 ± 53.29	887.06 ± 34.01
8	66.69 ± 0.95	67.52 ± 0.52	1026.89 ± 89.03	1040.70 ± 35.20
9	70.35 ± 0.56	70.87 ± 0.47	1117.00 ± 44.07	1140.17 ± 50.07
10	71.45 ± 1.07	71.70 ± 0.82	1189.40 ± 80.45	1159.75 ± 52.55
11	73.41 ± 0.81	72.36 ± 0.54	1171.88 ± 83.25	1120.87 ± 41.07
12	73.78 ± 1.32	74.47 ± 0.77	1121.40 ± 35.41	1220.28 ± 32.72

[a] $X \pm SE$, where X = mean and SE = standard error.

Subsample 1, Hypothesis 1

Evidence from the fully-restricted subsample (n = 45) was insufficient for the purpose of accepting or rejecting the hypothesis that protein and calorie intakes would be more closely associated with body size measurements than fat or carbohydrate intakes. The regression of intake variables on recumbent length and arm muscle area resulted in models which accounted for little variability in these two dependent measures (r^2 = .038 and .093, respectively). The relative contribution of individual nutrients was evaluated through examination of regression coefficients associated with separate intake parameters in regression models. Sums of squares were partitioned according to a SAS Type III procedure (SAS Institute, 1985) in which the contribution of each independent variable was examined in light of a "full model" which already included effects of all other independent variables. Strong evidence in favor of the null hypotheses that individual regression coefficients were equal to zero (p-values ranging from .301 to .939) precluded evaluation of individual nutrient contributions.

When recall restrictions were removed and subsample size increased from 45 to 145, no improvement was seen in r^2 values or p-values associated with individual regression coefficients. A sole exception was increased evidence for

rejection of the null hypothesis that the regression coefficient associated with protein intake was equal to zero, given a SAS Type III sums of squares model (SAS Institute, 1985) regressing intake on recumbent length ($p = .108$, compared with an earlier value of $p = .665$).

Subsample 1, Hypothesis 2

Results of t-test procedures on the fully-restricted subsample ($n = 45$) provided minimal evidence in favor of the hypothesis that accelerated growth would be associated with higher protein and calorie intakes than delayed growth (Table 5). As an indicator of above-mean and below-mean caloric intake, recumbent length appeared to be a more sensitive indicator than arm muscle area at these early ages.

When recall restrictions were removed, and accelerated/delayed groups redrawn from a subsample of $n = 145$, intake differences became much sharper for growth-altered groups, as long as those groups were defined in terms of recumbent length (Table 6). When arm muscle area was used as a basis of definition, however, expansion of subsample size did not sharpen intake differences.

TABLE 5

t-Tests Comparing Nutrient Intake of Growth-Accelerated and Growth-Delayed Infants

Dependent Variable = Recumbent Length (cm)		
NUTRIENT	ACCELERATED GROWTH (n = 5)	DELAYED GROWTH (n = 6)
Protein (grams)	46.30 ± 11.35[a]	43.81 ± 9.91
Calories	1186.97 ± 238.02	1108.19 ± 130.06

	PROTEIN	CALORIES
T :	.1655[b]	T : .3047[b]
p > |T| :	.8722[c]	p > |T| : .7675[c]

Dependent Variable = Arm Muscle Area (mm^2)		
NUTRIENT	ACCELERATED GROWTH (n = 8)	DELAYED GROWTH (n = 8)
Protein (grams)	44.24 ± 7.97	38.48 ± 4.50
Calories	998.13 ± 164.84	977.08 ± 67.28

	PROTEIN	CALORIES
T :	.6291[b]	T : .1182[d]
p > |T| :	.5394[c]	p > |T| : .9076[c]

[a] X ± SE, where X = mean and SE = standard error.

[b] An approximate T statistic for testing the null hypothesis that the means of two groups are equal, computed according to methods described in SAS Institute (1985). Except where otherwise noted, equality of sample variances was assumed, based on results of a SAS *F'* (folded) test (SAS Institute, 1985) yielding high probabilities against acceptance of the null hypothesis of equality.

[c] Probability of a greater absolute value of T under the null hypothesis.

[d] Assuming inequality of variances based on a SAS *F'* test (SAS Institute, 1985) yielding a probability of .031 against acceptance of the null hypothesis of equality.

TABLE 6

t-Tests Comparing Nutrient Intake After Removal of Recall Restrictions on Subsample 1

Dependent Variable = Recumbent Length (cm)		
NUTRIENT	ACCELERATED GROWTH (n = 23)	DELAYED GROWTH (n = 21)
Protein (grams)	44.39 ± 3.93[a]	33.79 ± 4.32
Calories	1089.89 ± 71.77	897.92 ± 77.50
	PROTEIN	CALORIES
T :	1.8181[b]	1.8201[b]
p > |T| :	.0762[c]	.0759[c]

[a] X ± SE, where X = mean and SE = standard error.
[b] An approximate T statistic for testing the null hypothesis that the means of two groups are equal, computed according to methods described in SAS Institute (1985), and based on results of a SAS *F'* (folded) test (SAS Institute, 1985) yielding high probabilities against acceptance of the null hypothesis of equality.
[c] Probability of a greater absolute value of T under the null hypothesis.

Subsample 1, Hypothesis 3

Because no infants in the fully-restricted subsample were fed either cow's milk or breast milk alone, the hypothesis that protein and calorie intakes would be higher in cow's milk feedings than in formula feedings, and higher in formula feedings than in breast milk feedings could not be tested directly. Profiles of infants according to method-of-feeding did allow for indirect comparisons, however, between infants fed varying combinations of

formula, breast milk, and whole cow's milk. Frequencies for combined methods-of-feeding in the fully-restricted (n = 45) subsample are presented on a month-by-month basis in Table 7.

TABLE 7

Frequencies for Combined Methods-of-Feeding by Age

TYPE OF FEEDING	AGE IN MONTHS							
	6	7	8	9	10	11	12	6-12
Formula + Whole Cow's Milk	0	0	1	1	2	1	0	5
Formula + Breast Milk	1	2	1	1	1	1	3	10
Formula Only	1	1	3	3	3	5	4	20
Breast + Formula + Whole Cow's	0	0	0	0	2	0	2	4
Other[b]	0	1	1	0	0	1	3	6
Total	2	4	6	5	8	8	12	45

[a] Age in months.
[b] Nonfat milk solids, soy-based formula, and any liquids classified as "other" on NHANES II questionnaires.

Mean protein and calorie intakes for combined methods-of-feeding are presented in Table 8. For both nutrients, intake was higher in whole-cow's-milk-containing versus non-containing combinations. Interpretation of such differences, however, is seriously confounded by several

factors. Since no attempt was made to account for solid food intake in the present study, combination feeding of liquids in question may or may not be the source of ingested nutrients. In addition, attribution of nutrient differences to various liquid combinations may involve unwarranted assumptions about relative amounts of liquid intake. For example, although mean protein intake for formula-plus-whole-cow's-milk feedings is estimated at 53.92 ± 6.50 grams, some 15 grams higher than mean protein intake for formula-plus-breast-milk feedings (38.52 ± 4.08 grams), this difference could only be attributed to differences in breast versus cow's milk feedings if formula intake remained constant.

TABLE 8

Mean Nutrient Intake by Combined Methods-of-Feeding

FEEDING COMBINATION	n[a]	PROTEIN (grams)	CALORIES
Formula + Whole Cow's Milk	5	53.92 ± 6.50[b]	1178.23 ± 121.87
Formula + Breast Milk	10	38.52 ± 4.08	1018.38 ± 58.99
Formula Only	20	37.85 ± 4.06	976.54 ± 71.32
Breast + Formula + Whole Cow's	4	63.99 ± 6.08	1393.01 ± 213.12
Other[c]	6	34.37 ± 5.14	1023.56 ± 163.50

[a] Number in feeding combination group.
[b] X ± SE, where X = mean and SE = standard error.
[c] Nonfat milk solids, soy-based formula, and any liquids classified as "other" on NHANES II questionnaires.

Only two mothers in the subsample indicated that their infants were still being breast fed at the time of the NHANES II survey. For these two infants (ages 8 and 11 months), average protein and calorie intakes were estimated at 28.08 ± 5.01 grams and 1254.77 ± 267.26 calories, respectively.

Breast-plus-formula feedings were generally associated with greater protein intake than feedings of formula alone during months 10 through 12 of postnatal development, but with similar or lower protein intake during months 6 through 9. Mean monthly intakes of dietary protein for these two feeding groups are presented in Table 9. Estimates were based on the expanded (recall "relaxed") version of Subsample 1 (n = 145).

TABLE 9

Mean Protein Intake by Month for Select Feeding Groups

	TYPE OF FEEDING	
Months of Age	Formula Only	Breast + Formula
6	28.16 ± 0.15[a]	29.97[b]
7	32.07 ± 4.31	40.89 ± 5.36
8	46.32 ± 8.89	25.38 ± 5.30
9	39.59 ± 2.73	29.80 ± 3.02
10	38.61 ± 4.14	43.22 ± 9.87
11	30.56 ± 2.06	43.81 ± 8.29
12	36.84 ± 3.40	48.54 ± 4.67

[a] X ± SE, where X = mean and SE = standard error.
[b] Based on a single observation.

Mean protein and caloric intakes for formula-only and formula-plus-cow's-milk feedings were consistently higher than comparable median values reported by Montalto, Benson and Martinez (1985) for NHANES II infants of both sexes.

Subsample 2: Descriptive Data

Independent variables. Subjects were unequally distributed across the four-year age range, with 63% of the final subsample (175/276) being composed of five-year-old and six-year-old subjects. Of the remaining 37% (101/276), seven-year-olds outnumbered eight-year-olds by a margin of nearly 2:1 (62:39).

Mean protein and caloric intakes were similar at years five and six, and also at years seven and eight, but between these two age groupings, showed an increase of approximately 12% (Table 10). Mean protein and calorie intakes at seven years (64.72 $\pm$ 2.33 grams and 1798.28 $\pm$ 57.23 calories, respectively) were consistent with previously reported values for NHANES II females between the ages of six-to-eight years as determined by Carroll, Abraham, and Dresser (1983) (Table 10).

Dependent variables. Both standing height and arm muscle area showed consistent mean increases across the four-year timespan represented in Subsample 2 (Table 11). The ratio of sitting-to-standing height showed consistent

mean decreases, with a noticably larger decrease occurring between the ages of six and seven (Table 11). Ratios were consistent with previously published findings on NHANES I females (United States Department of Health and Human Services, 1981b). Annual means for standing height were consistent with smoothed 50th percentile values reported for female children in the United States (Hamill, Drizd, Johnson, Reed, & Roche, 1977). Arm muscle estimates were comparable in pattern to, but consistently higher than, values reported by Frisancho (1981) for NHANES I females.

TABLE 10

Mean Protein and Calorie Intake By Year

AGE (years)	n[a]	PROTEIN (grams)	CALORIES
5 yrs	80	59.10 ± 1.84[b]	1619.14 ± 38.45
6 yrs	95	57.79 ± 2.06	1609.70 ± 62.26
7 yrs	62	64.72 ± 2.33	1798.28 ± 53.82
8 yrs	39	69.15 ± 3.59	1808.58 ± 83.13
5-8 yrs	276	62.96 ± 1.10	1723.27 ± 28.27
NCHS[c]	415	64 ± 1.3	1807 ± 33

[a] Number in age group.
[b] X ± SE, where X = mean and SE = standard error. Variance estimates in this table were obtained through a SAS "SURREGR" procedure (Shah, 1984) which took into account both sampling weights and design effects in NHANES II data.
[c] X ± SE values for six-through-eight-year-old female infants in NHANES II as reported by Carroll et al. (1983).

TABLE 11

Mean Anthropometric Values By Year

AGE (years)	n*	HEIGHT (cm)	ARM MUSCLE AREA (mm^2)	SITTING:STANDING HEIGHT RATIO
5	80	109.08 ± .347[b]	1671.72 ± 19.32	.5566 ± .0012
6	95	112.89 ± .489	1720.35 ± 48.47	.5531 ± .0020
7	62	120.62 ± .670	1873.07 ± 40.00	.5426 ± .0014
8	39	124.73 ± .769	2076.75 ± 48.98	.5408 ± .0015

* Number in age group.
[b] X ± SE, where X = mean and SE = standard error. Variance estimates in this table were obtained through a SAS "SURREGR" procedure (Shah, 1984) which took into account both sampling weights and design effects in NHANES II data.

Subsample 2, Hypothesis 1

Statistical testing based on models regressing intake on body size provided evidence in favor of the hypothesis that protein and calorie intakes would be more closely associated with body size measurements than fat or carbohydrate intakes. Although the amount of total variability in anthropometric observations accounted for by intake variables was consistently small (r^2 values ranging from .032-.072), strong differences were observed in the significance of specific nutrient contributions to explained variability. Specific nutrient contributions were evaluated through the testing of null hypotheses which equated regression coefficients associated with separate intake parameters to zero. For fat and carbohydrate parameters,

evidence strongly favored acceptance of the null hypotheses that regression coefficients were equal to zero, i.e., that knowledge of fat and carbohydrate intakes contributed little to the overall level of explained variability in anthropometric observations provided by the intake model. For protein and protein-calorie parameters, however, the probability of no regression coefficient contribution was fairly small (p-values ranging from .010 to .117, except in one instance involving regression of intake variables on arm muscle area). As a possible explanatory factor in the variability of anthropometric observations, caloric intake appeared significant primarily in the context of protein-calorie interactions. Relationships described above are summarized in Table 12.

Subsample 2, Hypothesis 2

Results of *t*-test procedures provided consistent evidence in favor of the hypothesis that accelerated growth would be associated with higher protein and calorie intakes than delayed growth (Tables 13 through 15). Of the three types of anthropometric observations gathered for this age group (standing height, arm muscle area, and sitting-to-standing height ratio), standing height appeared to be the most sensitive indicator of above-mean and below-mean nutrient intake.

TABLE 12

Hypothesis Testing on Individual Regression Coefficients in Models Regressing Intake on Body Size

	Dependent Variable		
	Standing Height	Arm Muscle Area	Sit:Stand Ratio[a]
Nutrient	p-value[b]		
Protein	.041	.484	.082
Calories	.801	.165	.339
Carbohydrate	.818	.264	.331
Fat	.848	.160	.131
Protein*Calories[c]	.024	.010	.117

[a] The ratio of sitting height to standing height.
[b] The probability that an individual regression coefficient is equal to zero. All p-values were obtained through regression analyses using a SAS "SURREGR" procedure (Shah, 1984) which took into account both sampling weights and design effects in NHANES II data.
[c] Independent variable designating protein-calorie interactions.

TABLE 13

t-Tests Comparing Intake of Growth-Accelerated and Growth-Delayed Children (Dependent Variable = Standing Height)

NUTRIENT	ACCELERATED GROWTH (n = 45)	DELAYED GROWTH (n = 40)
Protein (grams)	64.69 ± 2.98[a]	56.93 ± 2.58
Calories	1747.16 ± 65.68	1597.50 ± 64.62

	PROTEIN	CALORIES
T :	1.9462[b]	1.6170[b]
p > |T| :	.0550[c]	.1097[c]

[a] X ± SE, where X = mean and SE = standard error.
[b] An approximate T statistic for testing the null hypothesis that the means of two groups are equal, computed according to methods described in SAS Institute (1985), and based on results of a SAS *F'* (folded) test (SAS Institute, 1985) yielding high probabilities against acceptance of the null hypothesis of equality.
[c] Probability of a greater absolute value of T under the null hypothesis.

TABLE 14

t-Tests Comparing Intake of Growth-Accelerated and Growth-Delayed Children (Dependent Variable = Arm Muscle Area)

NUTRIENT	ACCELERATED GROWTH (n = 38)	DELAYED GROWTH (n = 37)
Protein (grams)	58.41 ± 2.79[a]	55.80 ± 3.09
Calories	1633.35 ± 64.40	1592.75 ± 75.36

PROTEIN		CALORIES	
T :	.6272[b]	T :	.4104[b]
p > |T|:	.5325[c]	p > |T|:	.6828[c]

[a] X ± SE, where X = mean and SE = standard error.
[b] An approximate T statistic for testing the null hypothesis that the means of two groups are equal, computed according to methods described in SAS Institute (1985), and based on results of a SAS *F'* (folded) test (SAS Institute, 1985) yielding high probabilities against acceptance of the null hypothesis of equality.
[c] Probability of a greater absolute value of T under the null hypothesis.

TABLE 15

t-Tests Comparing Intake of Growth-Accelerated and Growth-Delayed Children (Dependent Variable = Sitting Height:Standing Height Ratio)

NUTRIENT	ACCELERATED GROWTH (n = 37)	DELAYED GROWTH (n = 29)
Protein (grams)	59.68 ± 3.29[a]	58.17 ± 2.96
Calories	1681.38 ± 76.64	1597.14 ± 71.93

PROTEIN		CALORIES	
T :	.3312[b]	T :	.7779[b]
p > |T|:	.2178[c]	p > |T|:	.3146[c]

[a] X ± SE, where X = mean and SE = standard error.
[b] An approximate T statistic for testing the null hypothesis that the means of two groups are equal, computed according to methods described in SAS Institute (1985), and based on results of a SAS *F'* (folded) test (SAS Institute, 1985) yielding high probabilities against acceptance of the null hypothesis of equality.
[c] Probability of a greater absolute value of T under the null hypothesis.

Section Two: Nutrition, Growth, and Sexual Maturation

Subsample 3: Descriptive Data

Of the 622 white females eighteen years-of-age or younger who reported occurrence of menarche, only 183 considered their 24-hour recall data to typify "usual intake" and to be unrelated to recent dietary changes. Of these 183, only 46 provided recall data within one year of menarche. These 46 women constituted the subsample of interest in Section Two.

Mean menarcheal age for all white females less than or equal to eighteen years-of-age (n = 622) was estimated at 12.39 $\pm$ 1.19 years (X $\pm$ SD). A slight increase in this value was observed following recalculation for the smaller, recall-restricted group (n = 46, X = 12.84 years, SD = 1.26 years).

Although reported range-of-occurrence for age of menarche in the larger (n = 622) sample of white females was 9-16 years, in the smaller, fully-restricted group, this age-range was narrowed to 11-16 years.

Subsample 3, Hypothesis 1

Evidence from the fully-restricted (n = 46) subsample provided evidence generally favoring the hypothesis that combined knowledge of growth and intake would better predict

age of menarche than knowledge of growth or intake alone. r^2 values were used as test criteria for this analysis, where r^2 was defined as the amount of variation in the dependent variable that could be accounted for by the model, and computed as the ratio of sums of squares for the model divided by sums of squares for the corrected total. A SAS "MAXR" option (SAS Institute Inc., 1985) requesting maximum r^2 improvements per stepwise addition of independent variables to the model was also used to determine best models regressing intake-growth combinations on menarcheal age.

Regressions of intake on menarche resulted in r^2 values no larger than .0867, even when all four intake parameters (protein, carboyhdrate, fat and calories) were considered. Regressions of anthropometric variables (height and arm muscle area) on age of menarche resulted in an r^2 value over twice as large (.1934). While this "growth-only" model produced a higher r^2 than any other two-variable model, "combination" models including one anthropometric and one intake variable were nearly as effective in accounting for variation in age of menarche. Best among these two-variable "combinations" was the combination "height-plus-fat" (r^2 = .1776). The addition of a single intake parameter to the two-variable "growth only"

model increased the amount of variability in age of menarche accounted for by a "growth only" model by as much as 26%. Table 16 presents the full range of r^2 values associated with various multi-parameter models.

TABLE 16

r^2 Values for Models Regressing Growth and Intake on Age of Menarche

Number of Variables	Name of Variables	R-SQUARE*
1	Height	.1417
1	Calories	.0299
1	Arm Muscle Area	.0179
1	Fat	.0177
1	Protein	.0008
2	Height/Arm Muscle Area	.1934
2	Height/Fat	.1776
2	Height/Calories	.1682
2	Height/Protein	.1428
2	Protein/Calories	.0819
2	Arm Muscle Area/Fat	.0401
2	Protein/Fat	.0369
2	Calories/Fat	.0307
3	Height/Arm Muscle/Fat	.2446
3	Height/Arm Muscle/Calories	.2289
3	Height/Protein/Calories	.2183
3	Height/Protein/Fat	.2140
3	Height/Arm Muscle/Protein	.1935
4	Height/Arm Muscle/Fat/Protein	.2772
4	Height/Arm Muscle/Protein/Cals	.2720
4	Height/Arm Muscle/Calories/Fat	.2449
4	Protein/Carbohydrate/Fat/Cals	.0867
6	Height/Arm Muscle/Protein/ Carbohydrate/Fat/Calories	.2848

* Defined as the amount of variation in the dependent variable (age of menarche) which was accounted for by the model, and computed as the ratio of sums of squares for the model divided by sums of squares for the corrected total.

Subsample 3, Hypothesis 2

Results of t-tests comparing protein and calorie intakes of maturationally-accelerated and maturationally-delayed females favored rejection of the hypothesis that accelerated sexual maturation would be associated with greater protein and calorie intake than delayed sexual maturation. While mean caloric intake was marginally higher in the maturationally-accelerated group, mean protein intake was actually lower (Table 17). When recency-of-recall was

TABLE 17

t-Tests Comparing Intake of Maturationally-Accelerated and Maturationally-Delayed Adolescents (n = 46)

NUTRIENT	ACCELERATED MATURATION[a] (n = 5)	DELAYED MATURATION[b] (n = 5)
Protein (grams)	60.25 ± 6.19[c]	69.06 ± 7.57
Calories	1974.47 ± 301.33	1754.51 ± 171.21

	PROTEIN	CALORIES
T :[d]	- .7272	.6796
p > |T|:[e]	.4791	.5079

[a] Age of menarche less than or equal to [X-SD], where X = mean and SD = standard deviation.
[b] Age of menarche greater than or equal to [X+SD], where X = mean and SD = standard deviation.
[c] X ± SE, where X = mean and SE = standard error.
[d] An approximate T statistic for testing the null hypothesis that the means of two groups are equal, computed according to methods described in SAS Institute (1985), and based on results of a SAS *F'* (folded) test (SAS Institute, 1985) yielding high probabilities against acceptance of the null hypothesis of equality.
[e] Probability of a greater absolute value of T under the null hypothesis.

removed as a screening variable for subject entry into Subsample 3, thereby increasing subsample size from 46 to 183, differences between groups became virtually nonexistent (Table 18).

TABLE 18

t-Tests Comparing Intake of Maturationally-Accelerated and Maturationally-Delayed Adolescents (n = 183)

NUTRIENT	ACCELERATED MATURATION[a] (n = 40)	DELAYED MATURATION[b] (n = 25)
Protein (grams)	68.57 ± 4.38[c]	69.74 ± 5.07
Calories	1871.33 ± 107.59	1881.56 ± 129.62

	PROTEIN	CALORIES
T :	- .1711[d]	- .0607[d]
p > |T| :	.8647[e]	.9523[e]

[a] Age of menarche less than or equal to [X-SD], where X = mean and SD = standard deviation.
[b] Age of menarche greater than or equal to [X+SD], where X = mean and SD = standard deviation.
[c] X ± SE, where X = mean and SE = standard error.
[d] An approximate T statistic for testing the null hypothesis that the means of two groups are equal, computed according to methods described in SAS Institute (1985), and based on results of a SAS *F'* (folded) test (SAS Institute, 1985) yielding high probabilities against acceptance of the null hypothesis of equality.
[e] Probability of a greater absolute value of T under the null hypothesis.

Section Three: Growth, Maturation, and Age-related Disease

Subsample 4: Descriptive Data

Approximately 78% of all NHANES II women 50-55 years-of-age (316/405) reported total cessation of menstrual cycles prior to date of examination. Of these 316 women, 265 were white and constituted the subsample of interest in Section Three.

Mean estimates for independent variables designed to quantify cumulative lifetime energy expenditure remained relatively constant on a year-to-year basis throughout the six-year period (Table 19).

TABLE 19

Mean Values for Expenditure-related Variables by Year

AGE[a]	REPRODUCTIVE LIFE SPAN[a]	NUMBER OF LIVE BIRTHS[a]	AGE OF MENARCHE[a]	WEIGHT[a,b] (kg)	HEIGHT (cm)
50	30.75 ± 1.01[b]	3.23 ± .28	13.20 ± .25	23.05 ± .44	160.85 ± .71
51	30.62 ± 1.01	3.51 ± .27	12.77 ± .25	24.13 ± .73	161.95 ± .82
52	31.53 ± 1.31	3.31 ± .35	12.96 ± .27	22.95 ± .60	161.19 ±1.07
53	33.49 ± 0.96	3.41 ± .28	12.70 ± .29	23.10 ± .47	160.47 ± .91
54	33.54 ± 1.39	2.89 ± .32	12.91 ± .24	23.67 ± .45	161.24 ±1.06
55	31.88 ± 0.54	2.91 ± .23	12.86 ± .22	22.82 ± .63	158.84 ± .78
T[c]	32.15 ± 0.37	3.24 ± .13	12.87 ± .11	23.33 ± .26	160.91 ± .38

[a] Age in years. For age 50, n = 29; age 51, n = 50; age 52, n = 50; age 53, n = 57; age 54, n = 53; age 55, n = 26; ages 50-55, n = 265.
[b] X ± SE, where X = mean and SE = standard error. Variance estimates in this table were obtained through a SAS "SURREGR" procedure (Shah, 1984) which took into account both sampling weights and design effects in NHANES II data.
[c] Total number of subjects, 50-55 years (n = 265).

None of the 265 subjects met "high expenditure" or "low expenditure" criteria as established prior to analysis. In addition, no hospitalizations for cancer or fractures were reported by these 50-55 year-old postmenopausal white females. The hypothesis that high energy expenditure across all major channels of resource allocation would be associated with greater incidence of later-life disease than low expenditure across these same channels could not be tested in the absence of such observations. However, since relationships between energy expenditure and later-life disease were of primary interest in the overall study, two additional steps were taken in order to explore possibilities in this area. First, the upper age limit on Subsample 4 was removed to yield a new subsample of 2,635 postmenopausal white females 50-75 years-of-age. Within this expanded subsample, 12 subjects reported recent hospitalization for cancer and 18 reported recent hospitalization for fracture. Despite this increase in observations on later-life disease, however, hypothesized relationships between disease and energy expenditure remained untestable since the number of subjects who met expenditure criteria remained extremely low (n = 4). Of these four subjects, none reported hospitalization for fracture and only one (in the "low expenditure" category) reported hospitalization for

cancer. All mean values for expenditure-related variables in both groups of hospitalized subjects differed from overall subsample means by less than 10% (Table 20).

TABLE 20

Mean Values for Expenditure-related Variables by Hospitalization

EXPENDITURE-RELATED VARIABLE	n[a]	MEAN ± SE[b]	% DIFFERENCE[c]
Recent Hospitalization for Cancer			
Reproductive Lifespan (years)	12	31.14 ± 2.56	+ 2%
Number of Live Births	9	3.21 ± 1.08	- 9%
Age of Menarche (yrs)	12	13.32 ± 0.59	+ 4%
Weight[3,4] (kg)	12	22.36 ± 0.81	- 7%
Height (cm)	12	157.45 ± 1.73	- 3%
Recent Hospitalization for Fracture			
Reproductive Lifespan (yrs)	17	29.86 ± 1.62	- 2%
Number of Live Births	12	3.52 ± 0.34	0%
Age of Menarche (yrs)	17	13.34 ± 0.36	+ 4%
Weight[3,4] (kg)	18	23.90 ± 0.77	- 1%
Height (cm)	18	161.20 ± 1.09	0%

[a] Number of observations.
[b] standard error.
[c] $\frac{\text{[Total Subsample Mean]} - \text{[Hospitalization-Related Mean]}}{\text{[Total Subsample Mean]}}$

A second attempt to explore expenditure-disease relationships involved not only removal of the upper age limit from Subsample 4, but also alteration of the criteria for subject entry into high and low expenditure groups.

Instead of limiting expenditure groups to subjects falling a full standard deviation above or below the mean on each of five expenditure-related variables, expenditure groups were expanded to include all subjects falling above or below the mean on all five variables. Two hundred forty-seven subjects met these "relaxed" criteria; twenty-nine qualified for the high expenditure group, and 218 for the low expenditure category. Means for both groups are presented in Tables 21 and 22. While no cancer-related or fracture-related hospitalizations were reported for the high expenditure group, four subjects in the low expenditure category reported hospitalization for cancer and one subject reported hospitalization for fracture.

TABLE 21

Mean Values for Expenditure-related Variables After "Relaxation" of Expenditure Criteria

HIGH ENERGY EXPENDITURE		
EXPENDITURE-RELATED VARIABLE	n[a]	MEAN ± SE[b]
Reproductive Lifespan (years)	29	38.35 ± 0.79
Number of Live Births	29	5.22 ± 0.25
Age of Menarche (years)	29	11.65 ± 0.09
Weight[3,4] (kg)	29	27.98 ± 0.63
Height (cm)	29	165.22 ± 0.51

[a] Number of observations.
[b] Standard error.

TABLE 22

Mean Values for Expenditure-related Variables After "Relaxation" of Expenditure Criteria

LOW ENERGY EXPENDITURE		
EXPENDITURE-RELATED VARIABLE	n*	MEAN ± SE°
Reproductive Lifespan (years)	218	26.09 ± 0.44
Number of Live Births	176	1.90 ± 0.07
Age of Menarche (years)	218	14.32 ± 0.14
Weight$^{3/4}$ (kg)	218	20.23 ± 0.13
Height (cm)	218	155.03 ± 0.29

* Number of observations.
° Standard error.

Discussion

Outcome of the Analysis with Respect to an Overall Conceptual Framework

The insufficient number of observations on age-related diseases in Subsample 4 not only interferred with analysis of relationships between energy expenditure and incidence of disease, but also precluded evaluation of the overall conceptual framework outlined in Chapter 2 of the study. Because increased incidence of fractures and malignant

neoplasms was established as the measure of "maladaptiveness" in organization of energy expenditure, the overall value of an expenditure framework for assessing relationships between nutrition and aging could not be determined. Possibilities for clarification of the aging process through consideration of entropy-based phenomena also went untested as a result of incomplete analysis in this section of the study. Despite inconclusiveness of findings at this overall conceptual level, however, results did contribute to an understanding of one specific component of the general framework. That component involved specification of relationships between developmental processes.

Specification of relationships between developmental processes. Results of analysis on Subsample 3 encouraged treatment of growth and maturation as independent parameters of development. If these two processes had been closely synchronized, and if menarcheal age had been a simple "by-product" of rate of growth, then knowledge of intake should not have contributed to explained variability in menarcheal age in models already including growth parameters. In these models, contributions of intake should have been subsumed within growth measurements, i.e., while knowledge of intake should have helped to account for variability in growth, growth alone should have accounted

for variability in its "by-product", menarcheal age. Since knowledge of intake consistently improved the amount of variability in menarcheal age explained by growth, the possible independence of growth and maturation as parameters of development was confirmed.

Implications for Conceptualization of Nutrition as a Health Factor in Development

Increased attention to macronutrients most directly involved in modulation of life history processes appeared justifiable on the basis of overall study results. More specifically, increased attention to the role of protein as a unique contributor to patterns of development seemed in keeping with analysis of intake by female infants, children, and adolescents in NHANES II.

Results of hypothesis testing which involved models regressing intake and growth on menarcheal age also left open the possibility that intake of dietary fat helps determine rate of sexual maturation. However, conjecture by Frisch (1983) about the role of adipose tissue as a determinant of menarche could not be addressed on the basis of these findings, since intake of dietary fat and deposition of adipose tissue remain not only distinct events, but also potentially unrelated ones.

Methodological Issues

Use of cross-sectional data. The absence of repeated measurements on which to base analyses of growth, maturation, and dietary intake placed significant restrictions on the scope of the study and on possible approaches to data analysis. For example, although careful subject screening for normalcy and recency of recalled dietary intake helped adjust for some of the shortcomings of single-recall data, it also reduced subsample size to the point of jepardizing variance estimates. Although this reduction was particularly severe in the case of Subsamples 3 (over 90% of the original subsample was lost), even in Subsamples 1 and 2, recall screening of subjects cut subsample size at least in half. In an analogous type of process, attempts to define "accelerated" and "delayed" rates-of-growth by examining subjects a full standard deviation above or below their age-appropriate anthropometric means resulted in acceptable growth-surrogate measures but excessively small growth-altered groups. Degrees of freedom available for variance estimation in subsequent *t*-test procedures were reduced accordingly. In summary, the attempt to utilize cross-sectional data as means of investigating essentially longitudinal relationships may have been partially

responsible for the overall lack of statistically significant findings in the first two sections of the present study.

Treatment of reproductive variables. Questions about the methodological treatment of reproductive variables were also raised by results of the analysis. All three reproductive variables examined in subsample analysis (age of menarche, age of menopause, and number of live births) were initially treated as continuous and numeric. Yet observations for these reproductive variables tended to cluster around two or three discrete values rather than dispersing into a normal distribution (Table 23). This accumulation of observations around a few discrete values suggested treatment of such variables as categorical rather than continuous. However, treatment of menarcheal age as a continuous dependent variable did not appear to confound analysis of growth and intake effects in the testing of Subsample 3, Hypothesis 1. Results of *t*-test procedures for Subsample 3, Hypothesis 2 (in which discrete values for menarcheal age were used to create the categorical dependent variable "rate of maturation") did not help to further elucidate this continuous-versus-categorical issue.

TABLE 23

Distribution of Observations for Reproductive Variables

	QUANTILES						
	99%	90%	75%	50%	25%	10%	1%
AGE OF MENARCHE	15[a]	14	13	12	12	11	10
	16[b]	15	13	13	12	11	11
AGE OF MENOPAUSE	53[c]	51	50	47	42	37	20
NUMBER OF LIVE BIRTHS	11[c]	6	4	3	2	1	0

[a] All values for this row indicate number of years and are based on a subsample size of n = 622.
[b] All values for this row indicate number of years and are based on a subsample size of n = 46.
[c] All values for this row are based on a subsample size of n = 265.

Finally, while greater specificity in reproductive determinations (e.g., self-report of menarcheal month as well as menarcheal year) would be likely to smooth resulting distributions, reliability of such observations would be highly questionable.

Substantive Issues

Nutrition and growth. In general, results of analyses on both infants (Subsample 1) and children (Subsample 2) implicated protein intake as a more prominent factor than caloric intake in determining rate of growth, as long as these two factors were considered on an independent basis. Considered interactively, protein and calories emerged as significant in analyses of 5-8 year-olds only, but small subsample size most likely precluded findings of statistical significance for younger subjects. The uniformally stronger evidence for interactive versus individual protein-calorie contributions to variation in rate of growth suggested that special attention be paid to such interactions in future research.

The general failure of intake models to account for substantial variation in anthropometric measurements was not suprising, given the critical role played by genetic factors in explanation of individual growth. Models incorporating parental parameters into nutrition-growth analyses would be expected to produce r^2 values much larger than those obtained in the present study.

As a potential indicator of nutrient-altered rate of growth, recumbent length appeared to be more sensitive than arm muscle area in both 6-12 month-old and 5-8 year-old

subjects. For 6-12 month-old subjects, this finding was particularly unexpected, since the ability of arm muscle measurements to reflect nutritional modulation of growth had been previously demonstrated in this age group (Mills et al., 1986). However, since arm muscle measurements by Mills et al. were carried out on an all-male sample, i.e., a sample with potentially greater inter-individual variability in overall muscular development, gender differences may partially account for these differing results. The lesser sensitivity of arm muscle area as an indicator of nutrient-modulated rate of growth also raised questions about the influence of physical activity on nutrition-growth relationships. Since this critical developmental parameter was not included in the present study, it can only be speculated that differing amounts of physical activity for infants and children in Subsamples 1 and 2 may have resulted in differing rates of skeletal muscle synthesis for subjects with relatively similar protein and calorie intake.

The preponderance of older infants in Subsample 1 may also have worked to obscure nutrition-growth relationships in this group. Since over one quarter of all infants in Subsample 1 were in their twelvth month of life, more opportunity may have been provided for the occurrence of

"catch-up" and "catch-down" growth, i.e., genetically-influenced phenomena known to confound nutrition-growth relationships.

The role of feeding methods in early life as determining factors in protein and calorie intake was difficult to assess given the total absence of observations on subjects fed by a single method. In addition, because less than five percent of all subjects in Subsample 1 were still breast feeding at the time of the survey, assessment of breast feeding effects would have been difficult even in the presence of such observations.

The finding that breast-plus-formula feedings were associated with greater protein intake than formula feedings alone during months 10, 11, and 12, but with similar or lower protein intake during months 6 through 9 was also difficult to assess given lack of attention to solid food intake. One posible explanation for these findings, however, would involve speculation about the influence of solid foods in relationship to liquid feedings. Introduction of liquid formulas during the early months of life might be interpreted as replacing what would ordinarily be breast milk intake, whereas continuation of formula feedings during the later months of the first year might be

interpreted as postponing solid food intake rather than replacing intake of breast milk. The key difference in these interpretations would lie in predicted amounts of protein intake. As a breast milk replacement, intake of formula would be expected to result in net increases of dietary protein on a grams-per-milliliter basis, since both milk-based and water-based formulas are known to be higher than human milk in protein content when measured on this basis (Mead Johnson & Company, 1986; Pennington & Church, 1980; Schneider, Anderson & Coursin, 1983). As a factor delaying intake of solid foods, however, intake of formula might be expected to prompt net decrease in protein intake, given the generally higher protein content of these foods on a percentage weight basis. (The type of solid food intake which was "postponed" by continued feeding of formula would be a critical moderating factor in this overall equation, however.)

The finding of mean protein intakes well above the current RDA level, coupled with the finding of mean anthropometric values closely corresponding to 50th percentile growth standards developed from similar NCHS data, indicated that effects of excessive protein consumption on growth may have already been incorporated into present-day standards for growth as established for infants in the United States. If current growth standards

have in fact been "normed" on infants excessive in their intake of dietary protein, then such standards may make a highly questionable barometer in future studies of intake and its growth-related effects.

Nutrition, growth, and sexual maturation. Results from the testing of Hypotheses 1 and 2 in this section of the analysis were seen as producting somewhat conflicting results. The uniqueness of protein and calorie intakes as contributing factors to explained variability in menarcheal age was generally supported by the testing of Hypothesis 1. But the testing of Hypothesis 2 provided no evidence of aassociation between protein and calorie intakes and rate of sexual maturation.

Failure to incorporate a genetic parameter into this section of the analysis was seen as a potentially significant factor in the creation of this discrepancy. Because the best intake-growth model accounted for less than one third of the total variability in menarcheal age, genetic influences may have significantly confounded intake effects on rate of maturation by producing large variability in menarcheal age for subjects with very similar nutrient intakes. Such an interpretation would be consistent with the lack of intake differences produced by the testing of Hypothesis 2. In the testing of Hypothesis 1, however, the relative importance of protein and calorie intakes would not have been confounded by genetic parameters since examination

of variability in menarcheal age was already limited to the 30% range accounted for by intake-growth models. In short, potential consistencies in relationships between nutrition, growth, and sexual maturation may have been masked over by an approach to hypothesis testing which failed to standardize possible effects of genetic parameters.

The importance of protein-calorie interactions in studies of nutrition, growth, and maturation was underscored by results from the testing of Hypothesis 1. Not surprisingly, in models regressing intake on maturation, protein and calorie parameters accounted for greater variability in menarcheal age when combined than when considered in isolation. But more importantly, in models regressing both intake and growth on maturation, even after growth effects had been taken into account, the combined contribution of protein and calorie parameters was superior to their contribution when considered separately.

Growth, maturation, and age-related disease. Lack of difference between overall subsample means for expenditure-related variables and equivalent expenditure-related means for cancer-hospitalized and fracture hospitalized groups was not suprising, since formation of these hospitalized groups required elimination of an upper age limit on Subsample 4. By including 55-75 year-olds in the subsample, relationships between energy expenditure and

the incidence of disease were most likely confounded by the inclusion of subjects for whom expenditure played no significant role in disease onset.

Differences in mean age of menarche for 50-55 year-olds in Subsample 4 versus 11-15 year-olds in Subsample 3 were in keeping with secular trends toward earlier age of menarche. For Subsample 3 females born in the 1970's and 1980, mean age of menarche (12.39 $\pm$ 1.19 years) occurred .38 years earlier than mean age of menarche for Subsample 4 females born in the 1920's and 1930's (12.77 $\pm$ .33 years). However, since standard errors associated with these two means were equal to or larger than the difference between them, any conclusions about trends in menarcheal age based on such findings would be highly questionable.

Given the lack of opportunity to carry out hypothesis testing on Subsample 4, appropriateness of variables chosen to represent energy expenditure and age-related disease was difficult to assess. However, one methodological finding in this section of the study may have relevance for future research. Since relaxation of expenditure criteria to above-mean and below-mean levels still resulted in widely differing mean values for high and low expenditure groups, the more stringent X $\pm$ SD criteria appeared unnecessary for adequate differentiation of these groups. Above-mean and below-mean cutpoints in future studies would allow for

greater subsample size, and potentially more powerful testing of energy expenditure-disease relationships.

CHAPTER V

SUMMARY AND RECOMMENDATIONS

Summary

The purpose of the present study was threefold: (a) to describe a comprehensive conceptual framework for evaluating effects of nutrition on aging; (b) to explore the implcations of such a framework for developmental nutrition and research in dietary restriction; and (c) to test the viability of this conceptual framework through analysis of data collected on human subjects. The study was viewed as both theoretical and exploratory. Primary interest was focused on thematic and conceptual relationships rather than clinical or experimental issues.

Description of a conceptual framework and exploration of its implcations were carried out through reviews of literature involving dietary restriction, dietary allowances, physics, ecology, evolutionary biology, and anthropology. Testing of the framework was accomplished through secondary analysis of NHANES II - the Second National Health and Nutrition Examination Survey conducted from 1976-1980 by the National Center for Health Statistics [NCHS] in Hyattsville, Maryland.

Description of a comprehensive conceptual framework for evaluating effects of nutrition on aging was seen as involving four specific conceptual tasks: (a) clarification of the aging process; (b) specification of relationships between parameters of development; (c) elaboration of principles governing the course of development; and (d) consideration of aging within a specifically human context. Entropy research in the field of physics was viewed as providing a theoretical basis for clarification of the aging process. Analysis of resource allocation in the fields of ecology and evolutionary biology was seen as an appropriate starting point for specification of relationships between developmental processes, as well as for elaboration of principles governing development. Anthropological research focusing on the issue of neoteny served as the basis for consideration of aging within a specifically human context.

Description of a conceptual framework was determined to hold two basic implications for developmental nutrition. These implications included reassessment of criteria used to determine macronutrient allowances, and increased focusing of attention on macronutrients most directly involved in modulation of life history processes. Implications for research in dietary restriction included reformulation of baseline conditions, more careful timing of restriction, and

better differentiation of later-life events in experimental analyses of nutrition and aging.

Testing of the conceptual framework involved extraction of four age-related subsamples from NHANES II. Subsample 1 consisted of 45 white female infants ages 6-12 months whose 24-hour dietary recalls met pre-established normalcy criteria. Subsample 2 consisted of 276 white females ages 5-8 years whose recalls also met normalcy criteria. Subsample 3 consisted of 46 postmenarcheal white females ages 11-15 years whose 24-hour recalls had been pre-screened for both normalcy and recency. Subsample 4 consisted of 265 postmenopausal white females ages 50-55 years.

Six specific research hypotheses were tested using the four subsamples described above. Results of hypothesis testing included the following findings:

1. Dietary intake accounted for a very small amount (3-9%) of the total variability in anthropometric measurements for 6-12 month-old and 5-8 year-old subjects. Within this narrow range of explained variability, however, significance levels ranging from .010 to .117 pointed to protein-calorie interactions as the most important dietary factor in accounting for anthropometric variability. After testing of five models which regressed dietary intake on body size, only protein and protein-calorie paramaters were determined to be be significant contributing factors to variability in body size measurements at the .05 level.

2. For 5-8 year-old subjects, accelerated growth was associated with higher protein intake than delayed growth at the .06 level of significance, and with higher caloric intake at the .11 level. Exceedingly small subsample sizes (n = 11, n = 18) were implicated in the failure to observe similar relationships between intake and rate of growth in 6-12 month-old subjects.

3. Absence of clear-cut feeding groups for 6-12 month-old subjects precluded testing of the hypothesis that protein and calorie intakes would be higher in cow's milk feedings than in formula feedings, and higher in formula feedings than in breast milk feedings. However, a trend toward higher intake of both protein and calories was observed for cow's milk-containing versus non-containing feeding combinations.

4. While dietary and anthropometric factors combined to explain a relatively small amount of the total variability in menarcheal age (28%), models combining these two factors accounted for greater variability in menarcheal age than models of comparable size which contained either factor alone. Substitution of height and arm muscle area for fat and carbohydrate parameters of a four-variable model containing protein and calorie parameters was determined to

increase the amount of explained variability in menarcheal age from 8 to 27 percent.

5. Accelerated sexual maturation was not associated with significantly greater protein and calorie intakes than delayed sexual maturation. In terms of protein intake, maturationally-accelerated and maturationally-delayed groups were separated by only 1.5 grams, and in terms of energy intake, by only 84 calories.

6. Total absence of subjects meeting "high expenditure" and "low expenditure" criteria prevented testing of the hypothesis that high energy expenditure across all major channels of resource allocation would be associated with greater incidence of later-life disease than low expenditure across these same channels. An insufficient number of observations on age-related disease for 50-55 year-old subjects also precluded evaluation of the overall conceptual framework described in the present study. The relevance of entropy-based phenomena and expenditure frameworks for clarification of the aging process also went unresolved as a result of insufficient observations in this section of the analysis.

Recommendations

Adoption of an interdisciplinary approach to nutrition-aging research was viewed as a valuable step in in the present study, and is recommended to future investigators of nutrition and aging. Within this interdisciplinary framework, conceptualization of basic issues was observed to have not only theoretical ramifications, but experimental ramifications as well. The necessity for conceptual clarity in future research cannot be overstated.

Use of longitudinal data to test relationships between nutrition, development, and aging would correct for a number of limitations imposed on the present study by the use of cross-sectional data. Longitudinal data would allow for direct measurement of developmental parameters rather than indirect measurement of these parameters through surrogate variables. Adjustments for individual growth tempo would also be possible given the use of such data. The problem of intra-individual variability in dietary intake would be lessened by the presence of repeated dietary measurements, and the validity of reproductive data would become far less questionable since reproductive events would be recorded at the time of their occurrence.

Incorporation of genetic and physical activity parameters into future models of nutrition-aging relationships would also help to correct for a number of shortcomings in the present study. Inclusion of these parameters would help to place nutritional modulation of developmental processes within a more realistic context, and would partially eliminate these parameters as confounding sources of variability in models regressing intake on anthropometric or reproductive variables. Incorporation of genetic parameters might be accomplished through consideration of parental heights, weights, and reproductive histories. Self-report data on daily physical activities (cf., Satlin & Grimby, 1968) might be used to establish a physical activity parameter. Knowledge of physical activity would be particularly helpful in analyses involving observations on arm muscle area.

Increased attention to the role of protein as a modulating factor in nutrition-aging relationships is viewed as a key ingredient in the success of future research in this area. It is further recommended that the role of protein be considered in isolation from, and also in conjunction with, caloric intake. Successful analysis of these intake parameters during the first postnatal year must also include collection of data on solid food intake.

BIBLIOGRAPHY

Abraham, S. (1986). Analysis of data from a complex survey: the Health Examination Surveys. American Journal of Clinical Nutrition, 43, 839-843.

Ahmed, P.I. (Ed.). (1979). Toward a new definition of health. New York: Plenum.

Allen, L.H., Oddoye, E.A., & Margen, S. (1979). Protein-induced hypercalciuria: a longer term study. American Journal of Clinical Nutrition, 32, 741-749.

American Dietetic Association. (1981). Handbook of clinical dietetics. New Haven: Yale University Press.

American Psychological Association. (1983). Publication manual of the American Psychological Association (3rd ed.). Washington, D.C.: Author.

Anand, C.R., & Linkswiler, H.M. (1974). Effect of protein intake on calcium balance of young men given 500 mg calcium daily. Journal of Nutrition, 104, 695-700.

Armbrecht, H.J., Prendergast, J.M., & Coe, R.M. (Eds). (1984). Nutritional intervention in the aging process. New York: Springer-Verlag.

Asimov, I. (1966). Understanding physics. Vol. 1. New York: Mentor.

Austin, C.R., & Short, R.V. (Eds.). (1982). Reproduction in mammals. Book 4. Reproductive fitness. Cambridge: Cambridge University Press.

Baldwin, B.T. (1921). The physical growth of children from birth to maturity. University of Iowa Studies in Child Welfare. Vol. 1. Iowa City: University of Iowa Press.

Balough, M., Kahn, H.A., & Medalie, J.H. (1971). Random repeat 24-hour recalls. American Journal of Clinical Nutrition, 24, 304-310.

Barrows, C.H., Jr., & Kokkonen, G.C. (1975). Protein synthesis, development, growth and life span. Growth, 39, 525-533.

Barrows, C.H., Jr., & Kokkonen, G.C. (1982). Dietary restriction and life extenstion - biological mechanisms. In: Moment, G.B. (Ed.). Nutritional approaches to aging research. Boca Raton: CRC Press.

Bazzarre, T.L., & Myers, M.P. (1979). The collection of food intake data in cancer epidemiology studies. Nutrition and Cancer, 1, 22-45.

Beaton, G.H., Milner, B.A., Corey, P., McGuire, V., Cousins, M., Stewart, E., de Ramos, M., Hewitt, D., Grambsch, P. V., Kassim, N., & Little, J.A. (1979). Sources of variance in 24-hour dietary recall data: implications for nutrition study design and interpretation. American Journal of Clinical Nutrition, 32, 2456-2559.

Beaton, G.H., Milner, J., McGuire, V., Feather, T.E., & Little, J.A. (1983). Source of variance in 24-hour dietary recall data: implications for nutrition study design and interpretation. Carbohydrate sources, vitamins, and minerals. American Journal of Clinical Nutrition, 37, 986-995.

Beauchene, R.E., Bales, C.W., Bragg, C.S., Hawkins, S.T., & Mason, R.L. (1986). Effect of age of initiation of feed restriction on growth, body composition, and longevity of rats. Journal of Gerontology, 41(1), 13-19.

Bergmann, R.L., & Bergmann, K.E. (1979). Nutrition and growth in infancy. In: Falkner, F., & Tanner, J.M. (Eds.). Human growth. Vol. 1. Principles and prenatal growth. New York: Plenum.

Bernard, C. (1957). An introduction to the study of experimental medicine. (H.C. Greene, Trans.). New York: Dover. (Original work published 1865)

Bertrand, H.A. (1983). Nutrition-aging interactions: life-prolonging action of food restriction. In: Rothstein, M. (Ed.). Review of biological research in aging. Vol. 1. New York: Alan R. Liss.

Besdine, R.W. (1982). The data base of geriatric medicine. In: Rowe, J.W., & Besdine, R.W. (Eds.). Health and disease in old age. Boston: Little, Brown & Co.

Billewicz, W.Z., Fellowes, H.M., & Hytten, C.A. (1976). Comments on the critical metabolic mass and age of menarche. Annals of Human Biology, 31(1), 51-59.

Blum, H.F. (1968). Time's arrow and evolution (3rd ed.). New Jersey: Princeton University Press.

Blumenthal, H.T. (Ed.). (1983). Handbook of diseases of aging. New York: Van Nostrand Reinhold.

Borkan, G.A., Hults, D.E., & Mayer, P.J. (1982). Physical anthropological approaches to aging. Yearbook of Physical Anthropology, 25, 181-202.

Brody, J.A., & Brock, D.B. (1985). Epidemiologic and statistical characteristics of the United States elderly population. In: Finch, C.E., & Schneider, E.L. (Eds.). Handbook of the biology of aging (2nd ed.). New York: Van Nostrand Reinhold.

Bronson, F.H. (1985). Mammalian reproduction: an ecological perspective. Biology of Reproduction, 32, 1-26.

Brooke, O.G. (1986). Energy needs in infancy. In: Fomon, S.J., & Heird, W.C. (Eds.). Energy and protein needs during infancy. Orlando: Academic Press.

Brooks, D.R., & Wiley, E.O. (1986). Evolution as entropy. Toward a unified theory of biology. Chicago: The University of Chicago Press.

Brown, W.T., Little, J.B., Epstein, J., & Williams, J.R. (1978). DNA repair defect in progeric cells. In: Bergsma, D., & Harrison, D.E. (Eds.). Genetic effects of aging. New York: Alan R. Liss.

Bryden, M.M. (1968). Control of growth in two populations of elephant seals. Nature, 217, 1106-1108.

Bullough, V.L. (1981). Age at menarche: a misunderstanding. Science, 213, 365-366.

Burger, J., & Gochfeld, M. (1985). A hypothesis on the role of pheromones on age of menarche. Medical Hypotheses, 17, 39-46.

Burrell, R.W.J., Healy, M.J.R., & Tanner, J.M. (1961). Age at menarche in South African Bantu schoolgirls living in the Transkei reserve. Human Biology, 33, 250-261.

Butte, N.F., & Garza, C. (1985). Energy and protein intakes of exclusively breastfed infants during the first four months of life. In: Gracey, M., & Falkner, F. (Eds). Nutritional needs and assessment of normal growth. Nestle Nutrition Workshop Series. Vol. 7. New York: Raven.

Calder, W.A. (1984). Size, function, and life history. Cambridge: Harvard University Press.

Calder, W.A. (1985). The comparative biology of longevity and lifetime energetics. Experimental Gerontology, 20, 161-170.

Calow, P. (1978). Life cycles. An evolutionary approach to the physiology of reproduction, development, and age-ing. London: Chapman and Hall.

Calow, P. (1979). The cost of reproduction - a physiological approach. Biology Reviews, 54, 23-40.,

Campbell, J. (1982). Grammatical man: information, entropy, language, and life. New York: Simon and Schuster.

Campbell, V.A., & Dodds, M.L. (1967). Collecting dietary information from groups of older people. Journal of the American Dietetic Association, 51, 29-33.

Carroll, M.D., Abraham, S., & Dresser, C.M. (1983). Dietary intake source data: United States 1976-80. Vital and Health Statistics, Series 11, Number 231, 12-20.

Cassirer, E. (1957). The philosophy of symbolic forms. Vol. 3. The phenomenology of knowledge. New Haven: Yale University Press.

Catel, J. (1953). Ein Beitrag zur Frage von Hirnentwicklung und Menschwerdung. Klin. Wschr., 31, 473-475. Cited in Gould, S.J. (1977). Ontogeny and phylogeny. Cambridge: The Belknap Press of the Harvard University Press.

Clutton-Brock, T.H., Guinness, F.E., & Albon, S.D. (1982). Red deer. Behavior and ecology of two sexes. Chicago: The University of Chicago Press.

Comfort, A. (1979). The biology of senescence (3rd ed.). New York: Elseview.

Committee on Diet, Nutrition, and Cancer. Assembly of Life Sciences. National Research Council. (1982). Diet, nutrition, and cancer. Washington, D .C.: National Academy Press.

Cowles, R.B. (1965). Hyperthermia, aspermia, mutation rates and evolution. Quarterly Review of Biology, 40(4), 341-367.

Cranshaw, L.I., Moffitt, B.P., Lemons, D.E., & Downey, J.A. (1981). The evolutionary development of vertebrate thermoregulation. American Scientist, 69, 543-550.

Cronk, C.E., & Roche, A.F. (1982). Race- and sex-specific reference data for triceps and subscapular skinfolds and weight/stature. American Journal of Clinical Nutrition, 35, 347-354.

Cummings, S.R., Kelsey, J.L., Nevitt, M., & O'Dodd, K.J. (1985). Epidemiology of osteoporosis and osteoporotic fractures. Epidemiologic Reviews, 7, 178-198.

Cutler, R.G. (1979). Evolution of human longevity: a critical overview. Mechanisms of Ageing and Development, 9, 337-354.

Cutler, R.G. (1984). Evolutionary biology of aging and longevity in mammalian species. In: Johnson, J.E. (Ed.). Aging and cell function. New York: Plenum.

Cutler, W.B., & Garcia, C-R. (1984). The medical management of menopause and premenopause. Their endocrinologic basis. Philadelphia: J.B. Lippincott.

Danker-Hopfe, H. (1986). Menarcheal age in Europe. Yearbook of Physical Anthropology, 29, 81-112.

Daughaday, W.H. (Ed.). (1981). Endocrine control of growth. New York: Elsevier.

Delaney, M.J. (1982). Mammal ecology. Glasgow: Blackie.

de Waard, F. (1975). Breast cancer incidence and nutritional status with particular reference to body weight and height. Cancer Research, 35, 3351-3356.

Dilman, V.M. (1981). The law of deviation of homeostasis and diseases of aging. (H.T. Blumenthal, Ed.). Boston: John Wright - PSG.

Dreizen,S., Spirakis, C.N., & Stone, R.E. (1967). A comparison of skeletal growth and maturation in undernourished and well-nourished girls before and after menarche. The Journal of Pediatrics, 70(2), 256-263.

Dye, C.J. (1984). Age-related changes in taste and smell that affect nutritional adequacy. In: Armbrecht, H.J., Prendergast, J.M., & Coe, R.M. (1984). Nutritional intervention in the aging process. New York: Springer-Verlag.

Economos, A.C. (1981). Beyond rate of living. Gerontology, 27, 258-265.

Edlin, H.L. (1976). Trees and man. New York: Columbia University Press.

Ellis, F.R., Holesh, S., & Ellis, J.W. (1972). Incidence of osteoporosis in vegetarians and omnivores. American Journal of Clinical Nutrition, 25, 555-558.

Falkner, F., & Tanner, J.M. (Eds.). (1979). Human growth. Vol. 1. Principles and prenatal growth. New York: Plenum.

Falkner, F., & Tanner, J.M. (Eds.). (1986). Human growth. (2nd ed.). Vol. 1. Developmental biology, prenatal growth. New York: Plenum.

Fomon, S.J. (1986). Protein requirements of term infants. In: Fomon, S.J., & Heird, W.C. (Eds.). Energy and protein needs during infancy. Orlando: Academic Press.

Fomon, S.J., & Heird, W.C. (Eds.). (1986). Energy and protein needs during infancy. Orlando: Academic Press.

Forthofer, R.N. (1983). Investigation of nonresponse bias in NHANES II. American Journal of Epidemiology, 117(4), 507-515.

Frank, D.W. (1976). Physiological data of laboratory animals. In: Melby, E.C., Jr., & Altman, N.H. (Eds.). Handbook of laboratory animal science. Vol. III. CRC Press: Cleveland.

Frisancho, A.R. (1974). Triceps skin fold and upper arm muscle size norms for assessment of nutritional status. American Journal of Clinical Nutrition, 27, 1052-1058.

Frisancho, A.R. (1981). New norms of upper limb fat and muscle areas for assessment of nutritional status. American Journal of Clinical Nutrition, 34, 2540-2545.

Frisancho, A.R. (1982). Reply to letter by Bishop et al. American Journal of Clinical Nutrition, 36, 557-560.

Frisch, R.E. (1974). A method of prediction of age of age of menarche from height and weight at ages 9 through 13 years. Pediatrics, 53(3), 384-390.

Frisch, R.E. (1978). Population, food intake, and fertility. Science, 199, 22-30.

Frisch, R.E. (1983). Fatness, menarche, and fertility. In: Golub, S. (Ed.). Menarche. Lexington, Massachussetts: Lexington Books.

Frisch, R.E., & Revelle, R. (1970). Height and weight at menarche and a hypothesis of critical body weights and adolescent events. Science, 169, 397-398.

Gardner, M.J., & Heady, J.A. (1973). Some effects of within-person variability in epidemiological studies. Journal of Chronic Diseases, 26, 781-795.

Garn, S.M., & Rohmann, C.G. (1966). Interaction of nutrition and genetics in the timing of growth and development. Pediatric Clinics of North America, 13, 353-379.

Glass, A.R., Dahms, W.T., & Swerdloff, R.S. (1979). Body fat at puberty in rats: alteration by changes in diet. Pediatric Research, 13, 7-9.

Glass, A.R., Harrison, R., & Swerdloff, R.S. (1976). Effect of undernutrition and amino acid deficiency on the timing of puberty in rats. Pediatric Research, 10, 951-955.

Golub, S. (Ed.). (1983). Menarche. Lexington, Massachussetts: Lexington Books.

Goodman, M.J., Grove, J.S., & Gilbert, F., Jr. (1978). Age at menopause in relation to reproductive history in Japanese, Caucasian, Chinese, and Hawaiian women living in Hawaii. Journal of Gerontology, 33(5), 688-694.

Goodrick. C.L. (1978). Body weight increment and length of life: the effect of genetic constitution and dietary protein. Journal of Gerontology, 33, 184-190.

Goodrick, C.L., Ingram, D.K., Reynolds, M.A., Freeman, J.R., & Cider, N.L. (1983). Differential effects of intermittent feeding and voluntary exercise on body weight and lifespan in adult rats. Journal of Gerontology, 38(1), 36-45.

Goss, R.J. (Ed.). (1972). Regulation of organ and tissue growth. New York: Academic Press.

Gould, S.J. (1977). Ontogeny and phylogeny. Cambridge: The Belknap Press of the Harvard University Press.

Gould, S.J. (1980). The panda's thumb. More reflections in natural history. New York: W.W. Norton.

Gracey, M.G., & Falkner, F. (1985). Nutritional needs and assessment of normal growth. Nestle Nutrition Workshop Series. Vol. 7. New York: Raven.

Gurney, J.M. (1969). The young child: protein-energy malnutrition. In: Human nutrition: a comprehensive treatise. Vol. 2. Nutrition and growth. Jelliffe, D.B., & Jelliffe, E.F.P. (Eds.). New York: Plenum.

Gurney, J.M., & Jelliffe, D.B. (1973). Arm anthropometry in nutritional assessment: nomogram for rapid calculation of muscle circumference and cross-sectional muscle and fat areas. American Journal of Clinical Nutrition, 26, 912-915.

Haas, J.D., & Flegal, K.M. (1981). Anthropometric measurements. In: Nutrition and cancer: etiology and treatment. Newell, G.R., & Ellison, N.M. (Eds.). New York: Raven.

Hamill, P.V.V., Drizd, T.A., Johnson, C.L., Reed, R.R., & Roche, A.F. (1977). NCHS growth curves for children from birth to 18 years. Vital and Health Statistics, Series 11, Number 165, 1-74.

Hamill, P.V.V., Johnson, C.L., & Lemeshow, S. (1973). Body weight, stature, and sitting height: white and Negro youths 12 to 17 years. Vital and Health Statistics, Series 11, Number 124.

Hamilton, W.D. (1966). The moulding of senescence by natural selection. Journal of Theoretical Biology, 12, 12-45.

Hart, R.W., & Turturro, A. (1985). Review of recent biological research on theories of aging. In: Rothstein, M. (Ed.). Review of biological research in aging. Vol. 2. New York: Alan R. Liss.

Haynes, S.G., & Feinleib, M. (Eds.). (1980). Second conference on the epidemiology of aging. United States Department of Health and Human Services, NIH Publication No. 80-969.

Heidecker, L. (1974). The effect of dietary protein and light cycle on sexual maturation: an interaction study. Ann Arbor: Xerox University Microfilms (74-19, 483).

Hershey, D. (1963). Entropy, basal metabolism, and life expectancy. Gerontologica, 7, 245-250.

Hershey, D. (1974). Lifespan - and factors affecting it. Springfield: Charles C. Thomas.

Hershey, D., & Wang, H-H. (1980). A new age-scale for humans. Lexington, Massachussetts: D.C. Heath & Co.

Heshmat, M.Y., Kaul, L., Kovi, J., Jackson, M.A., Jackson, A.G., Jones, G.W., Edson, M., Enterline, J.P., Worrell, R.G., & Perry, S.L. (1985). Nutrition and prostate cancer: a case-control study. The Prostate, 6, 7-17.

Himes, J.H. (1979). Secular changes in body proportions and composition. Monographs of the Society for Research in Child Development, 44, 28-58.

Holehan, A.M., & Merry, B.J. (1985). The control of puberty in the dietary restricted female rat. Mechanisms of Ageing and Development, 32, 179-191.

Inter-university Consortium for Political and Social Research (1984a). Health and Nutrition Examination Survey II, 1976-1980: total nutrient intake, food frequency and other related dietary data. (2nd ICPSR ed.). Ann Arbor: Author. (ICPSR 8103)

Inter-university Consortium for Political and Social Research (1984b). Health and Nutrition Examination Survey II, 1976-1980: anthropometric data. (2nd ICPSR ed.). Ann Arbor: Author. (ICPSR 8104)

Inter-university Consortium for Political and Social Research (1984c). Health and Nutrition Examination Survey II, 1976-1980: medical history ages 6 months - 11 years. (2nd ICPSR ed.). Ann Arbor: Author. (ICPSR 8182)

Inter-university Consortium for Political and Social Research (1984d). Health and Nutrition Examination Survey II, 1976-1980: medical history ages 12-74 years. (2nd ICPSR ed.). Ann Arbor: Author. (ICPSR 8183)

Inter-university Consortium for Political and Social Research (1984e). Health and Nutrition Examination Survey II, 1976-1980: health history supplement ages 12-74 years. (1st ICPSR ed.). Ann Arbor: Author. (ICPSR 8237)

Jafarey, N.A., Khan, M.Y., & Jafarey, S.N. (1970). Role of artificial lighting in decreasing the age of menarche. The Lancet, Aug. 29, 471.

Johnson, H.A. (Ed.). (1985). Relations between normal aging and disease. Aging. Vol. 28. New York: Raven.

Jonas, H. (1966). The phenomenon of life: towards a philosophical biology. New York: Delta.

Jones, D.Y., Nesheim, M.C., & Habicht, J-P. (1985). Influences in child growth associated with poverty in the 1970's: an examination of HANESI and HANESII, cross-sectional US national surveys'-3. American Journal of Clinical Nutrition, 42, 714-724.

Kass, L.R. (1985). Toward a more natural science. Biology and human affairs. New York: The Free Press.

Kelsey, J.L. (1979). A review of the epidemiology of human breast cancer. Epidemiology Reviews, 1, 74-100.

Kirkwood, T.B.L. (1985). Comparative and evolutionary aspects of longevity. In: Finch, C.E., & Schneider, E. L. (Eds.). Handbook of the biology of aging (2nd ed.). New York: Van Nostrand Reinhold.

Kissinger, D.G., & Sanchez, A. (1981). Dietary factors in early life associated with age of menarche. Federation Proceedings, Abs. 3637, 670.

Kleiber, M. (1947). Body size and metabolic rate. Physiology Reviews, 27, 511-541.

Kohn, R.R. (1985). Aging and age-related diseases: normal processes. In: Johnson, H.A. (Ed.). Relations between normal aging and disease. Aging. Vol. 28. New York: Raven.

Koplan, J.P., Annest, J.L., Layde, P.M., & Rubin, G.L. (1986). Nutrient intake and supplementation in the United States (NHANES II). American Journal of Public Health, 76, 287-289.

Kralj-Cercek, L. (1956). The influence of food, body build, and social origin on the age of menarche. Human Biology, 28(4), 393-406.

Krieger, I. (1982). Pediatric disorders of feeding, nutrition, and metabolism. New York: John Wiley & Sons.

Lindstedt, S.L., & Calder, W.A. (1981). Body size, physiological time, and longevity of homeothermic animals. Quarterly Review of Biology, 56(1), 1-16.

Liu, K., Stamler, J., Dyer, A., McKeever, J., & McKeever, P. (1978). Statistical methods to assess and minimize the role of intra-individual variability in obscuring the relationship between dietary lipids and serum cholesterol. Journal of Chronic Diseases, 31, 399-418.

Lotka, A.J. (1922). Contribution to the energetics of evolution. Proceedings of the National Academy of Sciences, 8, 147-151.

Lotka, A.J., (1945). The law of evolution as a maximal principle. Human Biology, 17(3), 167-194.

Lowrey, G.H. (1986). Growth and development of children (8th ed.). Chicago: Year Book Medical Publishers.

Madden, J.P., Goodman, S.J., & Guthrie, H.A. (1976). Validity of the 24-hour recall. Journal of the American Dietetic Association, 68, 143-147.

Malcolm, L. (1986). Protein-energy malnutrition and growth. In: Falkner, F.R., & Tanner, J.M. (Eds.). Human growth. Vol. 1. Princples and prenatal growth. New York: Plenum.

Malina, R.M. (1979). IV. Secular changes in size and maturity: causes and effects. Monographs of the Society for Research in Child Development, 44, 59-102.

Malina, R.M., Hamill, P.V.V., & Lemeshow, S. (1973). Selected body measurements of children 6-11 years, United States. Vital and Health Statistics, Series 11, Number 123.

Margen, S., Chu, J-Y, Kaufmann, N.A., & Calloway, D.H. (1974). Studies in calcium metabolism. 1. The calciuretic effect of dietary protein. American Journal of Clinical Nutrition, 27, 584-589.

Martin, C. (1985). Endocrine physiology. New York: Oxford University Press.

Masoro, E.J. (1984). Nutrition as a modulator of the aging process. The Physiologist, 27(2), 98-101.

Masoro, E.J. (1985a). Metabolism. In: Finch, C.E., & Schneider, E.L. (Eds.). Handbook of the biology of the biology of aging. New York: Van Nostrand Reinhold.

Masoro, E.J. (1985b). Nutrition and aging - a current assessment. Journal of Nutrition, 115(7), 842-848.

Masoro, E.J., Bertrand, H., Liepa, G., & Yu, B.P. (1979). Analysis and exploration of age-related changes in mammalian structure and function. Federation Proceedings, 38, 1956-1961.

Masoro, E.J., Yu, B.P., Bertrand, H.A., & Lynd, F.T. (1980). Nutritional probe of the aging process. Federation Proceedings, 39, 3178-3182.

Matsumoto, K. (1982). Secular acceleration of growth in Japanese and its social background. Annals of Human Biology, 9(5), 399-410.

May, R.M., & Rubenstein, D.I. (1982). Reproductive strategies. In: Austin, C.R., & Short, R.V. (Eds.). Reproduction in mammals. Book 4. Reproductive fitness. Cambridge: Cambridge University Press.

Mazess, R.B. (1982). On aging bone loss. Clinical Orthopedics, 165, 239-252.

McCay, C., & Crowell, M.F. (1934). Prolonging the life span. Scientific Monthly, 39, 405-414.

McCay, C.M., Crowell, M.F., & Maynard, L.A. (1935). The effect of retarded growth upon the length of life span and upon the ultimate body size. Journal of Nutrition, 10, 63-79.

McGee, D., Rhoads, G., Hankin, J., Yano, K., & Tillotson, J. (1982). Within-person variability of nutrient intake in a group of Hawaiian men of Japanese ancestry. American Journal of Clinical Nutrition, 36, 657-663.

McNeill, D., & Livsan, N. (1963). Maturation rate and body build in women. Child Development, 34, 25.

Mead, Johnson, & Company. (1986). Pediatric products handbook. Evansville: Author.

Medawar, P.B. (1952). An unsolved problem in biology. London: Lewis.

Melton, L.J., III., Wahner, H.W., Richelson, L.S., O'Fallon, W.M., & Riggs, B.L. (1986). Osteoporosis and the risk of hip fracture. American Journal of Epidemiology, 124(2), 254-261.

Meredith, H.V. (1963). Change in the stature and body weight of North American boys during the last 80 years. In: Lipsitt, L.P., & Spiker, C.C. (Eds.). Advances in child development and behavior. Vol. 1. New York: Academic Press.

Meredith, H.V. (1976). Findings from Asia, Australia, Europe, and North America on secular change in mean height of children, youths, and young adults. American Journal of Physical Anthropology, 44, 315-326.

Merry, B.J., & Holehan, A.M. (1979). Onset of puberty and duration of fertility in rats fed a restricted diet. Journal of Reproduction and Fertility, 57, 253-259.

Micozzi, M.S. (1985). Nurtition, body size, and breast cancer. Yearbook of Physical Anthropology, 28, 175-206.

Millar, J.S., & Zammuto, R.M. (1983). Life histories of mammals: an analysis of life tables. Ecology, 64(4), 631-635.

Mills, J.L., Shiono, P.H., Shapiro, L.R., Crawford, P.B., & Rhoads, G.G. (1986). Early growth predicts timing of puberty in boys: results of a 14-year nutrition and growth study. Journal of Pediatrics, 109, 543-547.

Minot, C.S. (1908). The problem of age, growth, and death. New York: G.P.Putnam's Sons.

Mitchell, C.O., & Lipschitz, D.A. (1982). Detection of protein-calorie malnutrition in the elderly. American Journal of Clinical Nutrition, 35, 398-406.

Moment, G.B. (Ed.). (1982). Nutritional approaches to aging research. Boca Raton: CRC Press.

Monod, J. (1972). Chance and necessity: an essay on the natural philosophy of modern biology. New York: Vintage.

Montalto, M.B., Benson, J.D., & Martinez, G.A. (1985). Nutrient intakes of formula-fed infants and infants fed cow's milk. Pediatrics, 75(2), 343-351.

Morrison, S.D. (1983). Nutrition and longevity. Nutrition Reviews, 41(5), 133-142.

Morrison, S.D. (1984). Nutrition and longevity. In: Nutrition Reviews' present knowledge in nutrition. (5th ed.). Washington, D.C.: The Nutrition Foundation.

Murphy, R.S., & Michael, G.A. (1982). Methodoligic considerations of the National Health and Nutrition Examination Survey. American Journal of Clinical Nutrition, 35, 1255-1258.

Nakagawa, I., Sasaki, A., Kajimoto, M., Fukuyama, T., Suzuki, T., & Yamada, E. (1974). Effect of protein nutrition on growth, longevity, and incidence of lesions in the rat. Journal of Nutrition, 104, 1576-1583.

National Academy of Sciences. (1953). Recommended dietary allowances. National Research Council Publication No. 302. Washington, D.C.: Author.

National Academy of Sciences. (1958). Recommended dietary allowances. Revised 1958. National Research Council Publication No. 589. Washington, D.C.: Author.

National Academy of Sciences. (1964). Recommended dietary allowances (6th revised ed.). National Research Council Publication No. 1146. Washington, D.C.: Author.

National Academy of Sciences. (1968). Recommended dietary allowances (7th revised ed.). Washington, D.C.: Author.

National Academy of Sciences. (1974). Recommended dietary allowances (8th revised ed.). Washington, D.C.: Author.

National Academy of Sciences. (1980). Recommended dietary allowances (9th revised ed.). Washington, D.C.: Author.

National Research Council. (1943). Reprint and circular series No. 115. Washington, D.C.: Author.

National Research Council. (1945). Reprint and circular series No. 122. Washington, D.C.: Author.

National Research Council. (1948). Reprint and circular series No. 129. Washington, D.C.: Author.

Needham, J. (1933). On the dissociability of the fundamental processes in ontogenesis. Biology Reviews, 8, 180-223.

Nolen, G.A. (1972). Effect of various restricted dietary regimens on the growth, health, and longevity of albino rats. Journal of Nutrition, 102, 1477-1494.

Norwood, T.H., & Smith, J.R. (1985). The cultured fibroblast-like cell as a model for the study of aging. In: Finch, C.E., & Schneider, E.L. (Eds.). Handbook of the biology of aging (2nd ed.). New York: Van Nostrand Reinhold.

Otis, E.M., & Brent, R. (1954). Equivalent ages in mouse and human embryos. Anatomical Record, 120, 33-63.

Pennington, J.A., & Church, H.N. (1980). Food values of portions commonly used (13th ed.). New York: Harper and Row.

Peters, R.H. (1983). The ecological implications of body size. Cambridge: Cambridge University Press.

Phillips, H.T., & Gaylord, S. (Eds.). (1985). Aging and public health. New York: Springer.

Pianka, E.R. (1978). Evolutionary ecology (2nd ed.). New York: Harper and Row.

Pianka, E.R. (1981). Resource acquisition and allocation and acquisition among animals. In: Townsend, C.R., & Calow, P. Physiological ecology: an evolutionary approach to resource ecology. Sunderland, Massachussetts: Sinauer Associates.

Pike, R.L., & Brown, M.L. (1984). Nutrition: an integrated approach (3rd ed.). New York: John Wiley & Sons.

Pirkle, J.L., Schwartz, J., Landis, J.R., & Harlan, W.R. (1985). The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. American Journal of Epidemiology, 121(2), 246-258.

Rao, B.S.N., & Gopalan, C. (1984). Niacin. In: Nutrition Reviews' present knowledge in nutrition (5th ed.). Washington, D.C.: The Nutrition Foundation.

Richey, H.G. (1937). The relation of accelerated, normal, and retarded puberty to the height and weight of school children. Monographs of the Society for Research in Child Development, II(1).

Ries, W., & Pothig, D. (1984). Chronological and biological age. Experimental Gerontology, 19, 211-216.

Rifkin, J. (1980). Entropy: a new world view. New York: Viking.

Roche, A.F. (Ed.). (1979). Secular trends in human growth, maturation and development. Monographs of the Society for Research in Child Development, 44, 3-27.

Roff, D.A. (1985). Predicting body size with life history models. BioScience, 36(5), 316-323.

Romer, R.H. (1976). Energy: an introduction to physics. San Francisco: W.H. Freeman.

Ross, M.H. (1972). Length of life and caloric intake. American Journal of Clinical Nutrition, 25, 834-838.

Ross, M.H. (1977). Dietary behavior and longevity. Nutrition Reviews, 35, 256-265.

Ross, M.H., & Bras, G. (1965). Tumor incidence patterns and nutrition in the rat. Journal of Nutrition, 87, 245-260.

Ross, M.H., & Bras, G. (1971). Lasting influence of early caloric restriction on prevention of neoplasms in rats. Journal of the National Cancer Institute, 47, 1095-1113.

Ross, M.H., & Bras, G. (1975). Food preference and length of life. Science, 190, 165-167.

Ross, M.H., Lustbader, E., & Bras, G. (1976). Dietary practices and growth responses as predictors of longevity. Nature, 262, 548-553.

Rowe, D.A. (1983). Geriatric nutrition. Englewood Cliffs: Prentice-Hall.

Sacher, G.A. (1959). Relation of lifespan to brain weight and body weight. In: Wolstenholme, W.E., & O'Connor, M. (Eds.). The life-span of animals. Boston: Little, Brown.

Sacher, G.A. (1967). The complementarity of entropy terms for the temperature-dependence of development of aging. Annals of the New York Academy of Sciences, 138, 680-712.

Sacher, G.A. (1969). Evolution of the entropy and information terms governing mammalian longevity. Interdisciplinary Topics in Gerontology, 9, 69-82.

Sacher, G.A. (1982). Evolutionary theory in gerontology. Perspectives in Biology and Medicine, 25(3), 339-353.

Sadleir, R.M.F.S. (1969). The role of nutrition in the reproduction of wild mammals. Journal of Reproduction, Suppl. 6, 39-48.

Sanchez, A., Kissinger, D.G., & Phillips, R.I. (1981). A hypothesis on the etiological role of diet on age of menarche. Medical Hypotheses, 7, 1339-1345.

SAS Institute, Inc. (1985). SAS User's Guide: Statistics. Cary, N.C.: Author.

Satlin, B., & Grimby, G. (1968). Physiological analysis of middle-aged and old former athletes. Circulation, 38, 1104-1115.

Schelp, F.P., Pongpaew, P., Vudhivai, N., & Sornmani, S. (1986). Relationship of "weight for height" to "height for age" - a longitudinal study. Nutrition Research, 6, 369-373.

Schmidt-Nielson, K. (1984). Scaling. Why is animal size so important? Cambridge: Cambridge University Press.

Schneider, E.L., & Bynum, G.D. (1983). Diseases that feature alterations resembling premature aging. In: Blumenthal, H.T. (Ed.). Handbook of diseases of aging. New York: Van Nostrand Reinhold.

Schneider, H.A., Anderson, C.E., & Coursin, D.B. (Eds.). (1983). Nutritional support of medical practice (2nd ed.). Philadelphia: Harper and Row.

Schottenfeld, D., & Fraumeni, J.F., Jr. (1982). Cancer epidemiology and prevention. Philadelphia: W.B. Saunders.

Schwartz, J., Angle, C., & Pitcher, H. (1986). Relationships between childhood blood lead levels and stature. Pediatrics, 77(3), 281-288.

Setchell, B.P. (1978). The mammalian testis. Ithaca: Cornell University Press.

Shah, B.V. (1982). Standard errors of regression coefficient from sample survey data. Research Triangle Park, North Carolina: Research Triangle Institute.

Shah, B.V. (1984). SURREGR software for survey data analysis. American Statistician, 38, 68-89.

Shephard, R.J. (1986). Nutrition and the physiology of aging. In: Young, E.A. (Ed.). Nutrition, aging, and health . New York: Alan R. Liss.

Sherman, B., Wallace, R., Bean, J., & Schlabaugh, L. (1981). Relationship of body weight to menarcheal and menopausal age: implications for breast cancer risk. Journal of Clinical Endocrinology and Metabolism, 52, 488-493.

Short, R.V. (1982). Species differences in reproductive mechanisms. In: Austin, C.R., & Short, R.V. (Eds.). Reproduction in mammals. Book 4. Reproductive fitness. Cambridge: Cambridge University Press.

Shuttleworth, F.K. (1937). Sexual maturation and the physical growth of girls age six to nineteen. Monographs of the Society for Research in Child Development, II(5).

Shuttleworth, F.K. (1938). Sexual maturation and the skeletal growth of girls age six to nineteen. Monographs of the Society for Research in Child Development, III(5).

Shuttleworth, F.K. (1939). The physical and mental growth of girls and boys age 6 to 19 in relation to age at maximum growth. Monographs of the Society for Research in Child Development, IV(3).

Sober, E. (Ed.). (1984). Conceptual issues in evolutionary biology. Cambridge: MIT Press.

Sorabji, R. (1983). Time, creation, and the continuum. Ithaca: Cornell University Press.

Staszewski, J. (1977). Breast cancer and body build. Preventive Medicine, 6, 410-415.

Staszewski, J., & Czerwonej, A. (1971). Age at menarche and breast cancer. Journal of the National Cancer Institute, 47, 935-940.

Stearns, S.C. (1976). Life-history tactics: a review of the ideas. Quarterly Review of Biology, 51(1), 3-47.

Stini, W.A. (1971). Evolutionary implications of changing nutritional patterns in human populations. American Anthropologist, 73, 1019-1029.

Stini, W.A. (1975). Ecology and human adaptation. Dubuque: William C. Brown.

Stini, W.A. (1979a). Early nutrition, growth, disease, and human longevity. Nutrition and Cancer, 1(1), 31-39.

Stini, W.A. (Ed.). (1979b). Physiological and morphological adaptation and evolution. The Hague: Moulton.

Stini, W.A. (1981a). Association of early growth patterns with the process of aging. Federation Proceedings, 40, 2588-2594.

Stini, W.A. (1981b). Body composition and nutrient reserves in evolutionary perspective. World Review of Nutrition and Diet, 37, 55-83.

Stuchlikova, E., Juricova-Horakova, M., & Deyl, Z. (1975). New aspects of the dietary effect of life prolongation in rodents. What is the role of obesity in aging? Experimental Gerontology, 10, 141-144.

Szilard, L. (1959). On the nature of the aging process. Proceedings of the National Academy of Sciences, 45, 30-45.

Tanner, J.M. (1962). Growth at adolescence. Oxford: Blackwell Scientific.

Tanner, J.M. (1968). Earlier maturation in man. Scientific American, 218(1), 21-27.

Tanner, J.M. (1978). Foetus into man. Cambridge: Harvard University Press.

Tanner, J.M. (1981). A history of the study of human growth. Cambridge: Cambridge University Press.

Tanner, J.M. (1986). Physical development. British Medical Bulletin, 42(2), 131-138.

Tanner, J.M., & Davies, P.S.W. (1985). Clinical longitudinal standards for height and height velocity for North American children. Pediatrics, 107(3), 317-329.

Tollefsbol, T.O., & Cohen, H.J. (1986). Role of protein molecular and metabolic aberrations in aging, in the physiologic decline of the aged, and in age-associated diseases. JAGS, 34, 282-294.

Townsend, C.R., & Calow, P. (Eds.). (1981). Physiological ecology. An evolutionary approach to resource use. Sunderland, Massachussetts: Sinauer Associates.

Treoloar, A.E. (1981). Menstrual cyclicity and the pre-menopause. Mauritas, 3, 249-264.

Trotter, M., & Hixon, B.B. (1974). Sequential changes in weight, density, and percentage ash weight of human skeletons from an early fetal period through old age. Anatomical Record, 179, 1-18.

United States Department of Health and Human Services. (1981a). Plan and operation of the Second National National Health and Nutrition Examination Survey. Vital and Health Statistics, Series 1, No. 15. (DHHS Publication No. (PHS) 81-1317)

United States Department of Health and Human Services. (1981b). Basic data on anthropometric measurements and angular measurements of the hip and knee joints for selected age groups 1-74 years of age. Vital and Health Statistics, Series 11, No. 219. (DHHS Publication No. (PHS) 81-1669)

United States Department of Health and Human Services. (1982). A statistical methodology for analyzing data from a complex survey: the first National Health and Examination Survey. Vital and Health Statistics, Series 2, No. 92. (DHHS Publication No. (PHS) 82-1366)

United States Department of Health and Human Services. (1986). Nutrition monitoring in the United States. Hyattsville: Author. (DHHS Publication No. (PHS) 86-1255)

Vander, A.J., Sherman, J.H., & Luciano, D.S. (1980). Human physiology. The mechanisms of body function. (3rd ed). New York: McGraw-Hill.

Wachman, A., & Bernstein, D.S. (1968). Diet and osteoporosis. The Lancet, May 4, 958-959.

Walford, R.L. (1983). Maximum life span. New York: W.W. Norton.

Weast, R.C. (Ed.). (1985). CRC Handbook of chemistry and physics. 1985-1986. (66th ed.). Boca Raton: CRC Press.

Weil, A. (1983). Health and Healing. Boston: Houghton Mifflin.

Weindruch, R. (1985). Aging in rodents fed restricted diets. Journal of the American Geriatrics Society, 33(2), 125-132.

Weindruch, R.H., Kristie, J.A., Cheney, K.E., & Walford, R.L. (1979). Influence of controlled dietary restriction on immunologic function and aging. Federation Proceedings, 38(6), 2007-2016.

Weir, J.B. de. (1952). The assessment of the growth of schoolchildren with special reference to secular changes. Growth, 6, 19-33.

Widdowson, E.M. (1986). Discussion: protein need during infancy. In: Fomon, S.J., & Heird, W.C. (Eds.). Energy and protein needs during infancy. Orlando: Academic Press.

Widdowson, E.M., & McCance, R.A. (1960). Some effects of accelerating growth. I. General somatic development. Proceedings of the Royal Society of London, Series B, 152, 188-206.

Widdowson, E.M., & McCance, R.A. (1975). A review: new thoughts on growth. Pediatric Research, 9, 154-156.

Willett, W.C. (1987). Implications of total energy intake for epidemiologic studies of breast and large-bowel cancer. American Journal of Clinical Nutrition, 45, 354-362.

Wilson, M.F. (1983). Plant reproductive ecology. New York: John Wiley & Sons.

Wu, C.H. (1985). Current considerations of the menopause. Annals of Clinical and Laboratory Science, 15(3), 219-228.

Young, E.A. (Ed.). (1986). Nutrition, aging, and health. New York: Alan R. Liss.

Young, V.R. (1979). Diet as a modulator of aging and longevity. Federation Proceedings, 38, 1994-2000.

Yu, B.P., Murata, E.J., Bertrand, H.A., & Lynd, F.T. (1982). Life span study of SPF Fischer 344 male rats fed ad libitum or restricted diets: longevity, growth, lean body mass and disease. Journal of Gerontology, 37(2), 130-141.

Zacharias, L., Wurtman, R.J., & Schatzoff, M. (1970). Sexual maturation in contemporary American girls. American Journal of Obstetrics and Gynecology, 108(5), 833-846.

Zubay, G. (1983). Biochemistry. Reading, Massachussetts: Addison-Wesley.

Appendix

Nutrient Intake by Age for Infants in Subsample 1

PROTEIN (grams)				
Age in Months	n[a]	Original Subsample[b]	n[c]	Expanded Subsample[d]
6	(2)	29.09 ± 0.60[e]	(4)	32.74 ± 5.90
7	(4)	38.71 ± 6.26	(17)	33.92 ± 3.05
8	(6)	45.73 ± 10.95	(24)	33.02 ± 4.22
9	(5)	46.36 ± 9.23	(26)	39.00 ± 3.23
10	(8)	46.55 ± 6.35	(18)	47.24 ± 4.42
11	(8)	37.14 ± 2.83	(25)	36.03 ± 2.79
12	(12)	42.24 ± 4.67	(31)	43.60 ± 2.63
T[f]	(45)	41.46 ± 2.63	(145)	39.01 ± 1.40

CALORIES				
Age in Months	n[a]	Original Subsample[b]	n[c]	Expanded Subsample[d]
6	(2)	1082.09 ± 1.52[e]	(4)	1046.85 ± 57.91
7	(4)	792.08 ± 90.97	(17)	940.72 ± 73.03
8	(6)	1197.32 ± 160.38	(24)	968.61 ± 72.78
9	(5)	1107.96 ± 160.08	(26)	945.99 ± 72.61
10	(8)	1166.95 ± 139.32	(18)	1151.59 ± 88.17
11	(8)	1026.09 ± 125.22	(25)	910.04 ± 53.95
12	(12)	1046.11 ± 84.37	(31)	1040.83 ± 66.68
T[f]	(45)	1054.64 ± 50.51	(145)	995.86 ± 29.02

[a] Number in age bracket in Original Subsample (n = 45).
[b] Based on full recall restrictions (n = 45).
[c] Number in age bracket in Expanded Subsample (n = 145).
[d] After removal of recall restrictions (n = 145).
[e] X ± SE, where X = mean and SE = standard error.
[f] All subjects ages 6-12 months.