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DEVELOPMENT AND CHRONIC DISEASE: FUNCTIONAL ADAPTATION IN CYSTIC FIBROSIS

The Ohio State University PH.D. 1984

DEVELOPMENT AND CHRONIC DISEASE: FUNCTIONAL ADAPTATION IN CYSTIC FIBROSIS

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

Michael C. Mahaney, B.A., M.A.

* * * * *

The Ohio State University

1984

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This dissertation is fondly dedicated to Eleanor and Raymond, my parents; to Susan, my friend and spouse; and to Meghan, my daughter.

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FIELDS OF STUDY

Major Field: Biological Anthropology

Human Auxology: Studies in Human Growth and Development and Disease. Professors Michael D. Borden, Paul W. Sciulli, and Roy A. Tassava.

Biomedical Anthropology: Studies in Disease and Human Variation. Professors Michael D. Borden and Paul W. Sciulli.

Human Variation: Studies of Human Adaptability and Evolution in Contemporary Human Populations. Professor Paul W. Sciulli.

Studies in Biometrical Variation and Population Affinities in Prehistoric Amerindians. Professor Paul W. Sciulli.

TABLE OF CONTENTS

LIST OF TABLES

Table Page

LIST OF FIGURES

CHAPTER I

INTRODUCTION

The Problem

Strict reference to "normal" growth standards in the assessment of developmental status for individuals afflicted with chronic hereditary disorders may be misleading to students of biological variation and inappropriate as a guide for clinical evaluation in some cases. The patterns of development associated with such diseases may be either pathological results of disease involvement or functionally adaptive concomitants shared by those who inherit the disorders. As a functional adaptation the pattern of development serves to restore or maintain internal homeostasis in the face of some disruptive influence, such as chronic disease stress. This dissertation reports on the investigation of selected aspects of physical development in individuals with cystic fibrosis to (1) determine the existence of a pattern of development at variance with relevant standards and (2) discern whether such a variant pattern was indicative of pathology or functional adaptation. To accomplish this, the patterns of relationships among the developmental indicators

of dental, sexual, and skeletal maturation, disease severity, and chronological age were examined in fifty juvenile and adolescent subjects in a clinical setting.

Biological Anthropology and Auxology

As a subfield of anthropology, which is as much a way of studying phenomena as it is a delimiter of the phenomena to be studied, biological (nee physical) anthropology is characterized by the hallmarks of the parent discipline itself: a comparative approach which spans broad geographic and temporal ranges, an holistic perspective, and the necessary eclecticism and synthetic capabilities to examine the multifaceted subject matter of human diversity. Additionally, biological anthropology possesses, in the form of evolutionary theory, a testable philosphical foundation which directs and makes interpretable the efforts of researchers in what, at first notice, might appear to be widely disparate specializations. During the last few decades biological anthropology has experienced a shift from typological to populational perspectives in the study of human biological variation in space and time. The field has come to be typified more by attempts to understand the processes responsible for variation in contemporary human populations than by descriptions of the products of those processes (Katz, 1974, p. 304). This is not to suggest that description

has been, or should have been, eliminated from anthropological investigations. Rather, it remains an essential component of any study; one which serves to identify populational variance and indicate directions for profitable research regarding the processes underlying the phenotypic deviations from the mean.

This is equally true for anthropological research in the specialization of human biological growth and development, or human auxology. Auxological investigation has long been associated with American anthropology (Garn, 1980, p. 275); and in many European universities anthropology _is_ auxology (Garn, 1980; Tanner, 1978a). Not all research in human growth and development is anthropological nor done by biological anthropologists. Anatomists, biochemists, geneticists, nutritionists, pediatricians, physiologists, and many specialists in a host of biomedical disciplines may claim some aspect of human growth and development. However, it is with investigators doing what would today be referred to as biological anthropology that auxology got its start in Europe during the late eighteenth and early nineteenth centuries.

Although Scammon and Boyd (Boyd, 1980) knowledgeably trace interest in human growth and development to the ancient Mesopotamians (_ca_. 4000-50 B.C.) and many other auxologists refer to Aristotle, the scientific study of the subject is generally agreed to have begun

with the collaboration of Buffon and Montbeillard in eighteenth-century France (Tanner, 1978a, p. 516). Published in 1777 as the fourth supplement to Buffon's Natural History, Montbeillard's now famous longitudinal study of the growth of his son inspired many naturalists of the time to "see how children grow." Typical of the work of all competent natural historians during the late 1700s, that of Buffon and his auxological contemporaries was done with great diligence and care, noting such phenomena as the adolescent growth spurt, seasonal variations in growth velocities, diurnal variations in stature, and sex-specific growth differences (Tanner, 1978a, p. 518). Fastidious data collection and subsequent speculation marked the early auxological inquiries.

By the mid-nineteenth century, human auxology experienced a revolution which would not even touch the rest of biology until 1900. The Belgian mathematician and astronomer Quetelet introduced mathematics to growth and development (Tanner, 1978, p. 526). Intrigued by the concept of an ideal or representative type, Quetelet, in association with the French epidemiologist Villermé, conducted the first large-scale cross-sectional survey of children (Ackerknecht, 1952; Tanner, 1978a, p. 527). It was in the analysis of the data from this survey, and the ones which followed, that Quetelet made his most lasting impression on auxology. He discovered "that human stature

is distributed in many populations according to the law of error" (Hilts, 1973). The first to use mathematical expressions to express growth data, Quetelet was followed intellectually by many other nineteenth-century Europeans such as Villermé, Galton, Roberts, Chadwick, and Horner who each contributed to the auxological literature. Large-scale cross-sectional studies geared toward elucidating populational, socioeconomic, and health-related differences in growth became more common. This sort of epidemiological auxology was primarily a tool of politicians and social reformers. Occasionally a more basic sciences study, such as Galton's family likeness inquiry, would surface (Tanner, 1978a); but it was the cross-sectional growth survey, along with standard deviations and percentiles, which came to the United States in the late 1800s.

The cross-sectional surveys initiated in America utilized public school children as subjects for the most part. Large sample studies conducted by educators such as Bowditch (Boston, 1875) and Peckham (Milwaukee, 1882) were used initially to measure the effects of social class and economic conditions on development. Unexpectedly, these studies identified differences between immigrant children and those of established "American" families (Tanner, 1978a); a foreshadowing of anthropological investigations to come. Additionally, associations among

behavior, cognitive abilities, and growth were being elucidated by researchers such as Porter (1884). By the 1890s, the interest in growth among key people in several different disciplines had peaked in the United States; however, the technical skills and mathematical training, accessible primarily in Europe, necessitated the recruitment of scholars who, if not European, were at least educated on the continent.

According to legend, auxology and American anthropology became intertwined on a train bound for Cleveland, Ohio in 1888 (Tanner, 1978a, p. 576). The recruitment by Hall of Franz Boas, claimed by nearly every subfield of American anthropology, proved mutually beneficial to both areas of study. To a fledgling academic endeavor devoted to documenting all aspects of human variation, auxological methodologies and theories were a welcomed addition to the ethnological repertoire. Auxology, on the other hand, experienced a revolution in perspective from this merger. Auxological anthropologists digressed a bit from the large-scale social epidemiologies, amplified the comparative, holistic, and eclectic aspects of auxology, and exploited what, for the most part, were their own untapped data reserves: the peoples of "exotic" cultures (Garn, 1980, p. 276).

During the early 1900s, growth research by anthropologists like Boas introduced new concepts to auxology

such as that of physiological or developmental age, tempo of growth, and the relative value of longitudinal studies (Tanner, 1978a, pp. 576, 578). Students more firmly entrenched in physical anthropology, like West, Wissler, and Hrdlička, attacked the well-known auxological problems of the adolescent growth spurt; sex differences in growth; geographic, ethnic, and cultural differences in development; and the secular trend (Garn, 1980, p. 276; Stewart, 1973; Tanner, 1978a). These analyses were predominantly retrospective in design and descriptive in result.

In the second quarter of the century, new objectives surfaced. Prospective studies, "designed to obtain . . . information about particular population groups or segments of the population [employing] the longitudinal method" were initiated in several university cities, such as Boston, Cleveland, Denver, and Berkeley (Garn, 1980, pp. 276-77). These investigations contributed much to the literature concerning individual differences in growth rates and maturational timing, as well as to methodologies by which such differences might be ascertained. It was during this period that radiographic techniques for the evaluation of "bone age" and methods for the measurement of body composition were developed (Garn, 1980, 1981). By the middle of the twentieth century, the first longitudinal normative standards for a number of metric

and developmental variables were available for clinical and academic application (Garn, 1980, p. 277).

It was during the last three decades that growth and development, as a specialization of biological anthropologists, underwent changes experienced by the remainder of the subfield. Description, although not eliminated, was subjugated as a goal for auxology by problem-oriented growth research. The focus of most current studies is decidedly more narrow than those of the early 1900s. However, the implications of their findings are perhaps broader than ever before; impinging, not only on theories concerning the origins of adult human phenotypic variation and human evolution, but also on clinical, community, and international health care practices (see, e.g., Myrianthopoulos & French, 1968; Owen et al., 1974; Robinow, 1982).

Anthropologists involved in growth and development research are as likely to devote their energies to any one (or, oftentimes, a combination) of the following subject areas: prenatal growth and development (see, e.g., Gottlieb, 1984; Scott, 1978; Southgate, 1978), perinatal growth (e.g., Brandt, 1979; Johnston, 1978; Trevathan, 1984), or childhood and adolescent growth (e.g., Beunen et al., 1982; Bogin & MacVean, 1982; Kramer, 1983; Malina, 1978). Many auxological investigators concentrate on a particular aspect of growth and development,

such as craniofacial growth (e.g., Isreal, 1978; Krogman, 1974), changes in body composition during growth (e.g., Cronk et al., 1983; Johnston et al., 1982; Mukherjee & Roche, 1984), nutrition and growth (e.g., Coodin et al., 1980; Frisancho, 1978; Bueller & Pollitt, 1982), and/or the growth of dental and skeletal systems (e.g., Demirjian, 1978; Kimura, 1983; Roche, 1978). Additionally, a great percentage of current growth and development studies conducted within biological anthropology are comparative and, in increasing numbers, experimental (e.g., Pucciarelli, Oyhenart & Terreros, 1984).

Perhaps those studies which may be recognized most readily as anthropological in nature are those which are explicitly comparative in approach, dealing directly with problems of human biological variation in contemporary populations. Projects investigating the relationships among some aspect of the environment, growth and development, and interpopulational variation within the species come to mind in this context. Notable among these types of studies are those making direct comparisons among different populations or groups (e.g., the encyclopedic Eveleth & Tanner, 1976; Eveleth, 1978), those which elucidate patterns of growth and development in previously undescribed groups (e.g., Hiernaux, 1964; Little, Galvin & Mugambi, 1983; Johnston et al., 1984; Sato & Kitagawa, 1983), and those which examine growth and development in

populations inhabiting regions associated with climatic or environmental extremes (e.g., Beall, 1981; Frisancho, 1981; Haas, 1982). In addition, research directed toward documenting and understanding secular trends (e.g., Low, King & Leong, 1982; Van Wieringen, 1978), as well as interrelationships among pre- and postnatal growth variables and demographic parameters (e.g., Hunt & Newcomer, 1984; Scott & Bajema, 1982) is to be found within the repertoire of auxological anthropology. One feature which distinguishes these and related studies from those previously mentioned is the reliance upon many of the concepts and principles of current evolutionary theory. With the exception of the allometry studies (e.g., Cheverud, 1982; Shea, 1983; Steudel, 1982), they utilize the explanatory power of the theory to deal with microevolutionary change in ontogenetic variables.

Clinical Auxology and Biological Anthropology

Biological anthropologists have become increasingly involved in clinical auxology. The anthropological literature on effects of various disease experiences on human growth and development includes studies of the auxologic concomitants of congenital disorders (e.g., Angelov, Tomova & Ninova, 1980), chromosomal mutations (e.g., Abdel-Hameed, 1979; Aziz, 1981; Barden, 1983), inborn errors of metabolism and point mutations (e.g., Laor,

Garfunkel & Koyoumundjisky-Kaye, 1982; Laron et al., 1978; McCormack et al., 1976), infectious disease (e.g., Baumgartner & Pollitt, 1983; Jelliffe & Jelliffe, 1978; Miall, Desai & Standard, 1970), and chronic disorders of various etiologies (e.g., Hauspie, Susanne & Alexander, 1976). In many instances the contribution to a clinical understanding of growth disturbances by the application of the anthropological orientation have been significant (Garn, 1980; Robinow, 1982); as have been the clinical contributions, especially in the areas of clinical methodologies and skills, to biological anthropology. However, one area which has not been adequately examined, perhaps neglected, in these forays into clinical auxology, are the possible phylogenetic implications of developmental variation associated with some disease entities.

Typically, interactions between growth and development and disease have been considered solely within an ontogenetic framework. Although disease has long been recognized as a selective factor by biological anthropologists (see, e.g., Blumberg & Hesser, 1975; Livingstone, 1980), adaptations to disease stress have been hypothesized predominantly in the form of simply inherited, single locus traits rather than as complex polygenic ones, such as growth and development. Illness, whether acute, chronic, or congenital, has generally been viewed as a variable which produces certain untoward effects on

"normal" growth and development. With few exceptions (e.g., Aziz, 1981; Mueller & Pollitt, 1983), these effects are not perceived as having an hereditary component or identified phylogenetic implications. Likewise, no evolutionary consequences have been suggested by those who look upon disease entities as malign concomitants of a deficient socioeconomic, cultural, or psychological milieu which compromises inherited developmental programs (see, e.g., Greene & Johnston, 1980).

Ontogeny, Phylogeny, and Functional Adaptation

With the obvious exceptions of the works of scholars like Thompson (1961) and DeBeer (1930, 1958), the connections between ontogeny and phylogeny had been little explored since the general repudiation by Weismann's germ line theory of Haeckel's biogenetic law (Gould, 1977, pp. 1, 102-109). That ontogeny and phylogeny are related is an inescapable and, as Gould (1977, p. 2) notes, "unenlightening" conclusion. Nonetheless, although

> . . . [a] plausible argument could be made that evolution is the control of development by ecology . . . neither area has figured importantly in evolutionary theory since Darwin, who contributed much to each. This is being slowly repaired for ecology . . . but development is still severely neglected. (Van Valen, 1973, in Gould, 1977, p. 1)

An organism's phylogeny contributes the hereditary program for its growth and development. Aptive traits,

whether growth related or not, which have been altered during phylogeny must be expressed in ontogeny to affect a differential fertility vis-à-vis those traits. Therefore, phyletic information "must reside in the development of individuals" (Gould, 1977, p. 2). From the ontogenetic perspective evolution may occur in two general ways. Novel characters may be "introduced at any stage of development with varying effects upon subsequent stages, or . . . characters already present [may] undergo changes in developmental timing [heterochrony]" (Gould, 1977, p. 4).

Behind the phenomena of ontogeny are the genes. As such, those phenomena are subject to the influences of the various forces of evolution included within the neo-Darwinian paradigm (insofar as it predicts the changes over time in gene frequencies resulting from the "actions" of these forces). One of those forces, natural selection, has been historically paramount in the theoretical literature. Neither Darwin (1859) nor proponents of the modern synthetic theory of evolution perceived natural selection as the exclusive generator of evolutionary change (Ayala & Valentine, 1979; Futuyma, 1979; Lewontin, 1974). It has been agreed upon generally, however, to be the single mechanism capable of producing adaptation (Ayala & Valentine, 1979; Futuyma, 1979; Gould & Vrba, 1982). It is most important to note at this juncture that the term

adaptation is used here as a noun and therefore refers to "any transmissable characteristic of an organism that by its presence permits an interaction with the environment that causes its possessors to produce, on the average, more offspring . . . than would be produced in its absence" (Stern, 1970, p. 44). The salient features for the definition of adaptations, then, are (1) heritability, (2) association with positive differential fertility, (3) association with a particular environmental circumstance or set of circumstances, and (4) the existence of a known functional relationship between the trait and increased fitness (fertility) in that environment.

In contrast to the especially strict definition of adaptation briefly outlined above is a more general and less restrictive concept which emphasizes the functional consequences of adaptation on both the populational and individual levels (Mazess, 1975; Thomas, 1975). This view, which is usually considered far too lenient by many evolutionary biologists and those whose pursuits are primarily genetic, has been employed generically by several biological anthropologists to apply to "innumerable biological and social phenomena related to the achievement of relatively beneficial adjustments to the environment" (Bennett, 1979, p. 401). In this context adaptations are those features of organisms which not only augment the abilities of their possessors to survive specific

environmental conditions, but also facilitate the maintenance of physiological function and enhance reproductive performance in the face of those conditions. In its "generic" form adaptation is defined in terms of the three criteria indicated above: survival, maintenance, and reproduction. Additionally, for such traits to be considered adaptations, they must be demonstrated as "either relatively advantageous or, to some extent, necessary" (Bennett, 1979, p. 401). Such a perspective on adaptation has guided the majority of investigations into what biological anthropologists and human biologists prefer to call "human adaptability" (Collins & Weiner, 1977).

It should be evident that concordance concerning the use of the term adaptation is not ubiquitous among students of biological variation. Also, it should be clear that the provision of an explicit definition of adaptation in biological studies is by no means a trivial matter. Therefore, for the purpose of clarity, the more inclusive or generic concept of adaptation will be referred to as "functional adaptation" after Frisancho (1981). As such, the utilization of this term only implies the recognition of a trait's functionally beneficial or necessary contribution to an organism's survival, maintenance, and/or reproduction in response to environmental stressors. As a further delimiter, functional adaptation should be taken to refer to that class of

characters, indicated above, with a strongly heritable component and which are shared, not necessarily exclusively, by members of the population under study.

However, a demonstrable fitness-increasing function, the result of natural selection, should not be inferred from the use of the term "functional adaptation." Traits with that sort of hypothesized phylogenetic etiology will be labeled "genetic adaptations"; an approach explicitly consistent with that of Frisancho (1981) and implicitly consistent with others in this field of study (e.g., Dobzhansky, 1968; Lewontin, 1957; Mazess, 1975; McCutcheon, 1964; Thomas, 1975). Genetic adaptations, as described previously, are those features which Darwin saw as responsible for "the conversion of the variation among individuals . . . into variation between groups in space and time" (Lewontin, 1974, p. 4). Operationally, these responses may be further characterized by the fact that they require several generations to become established in a population.

Both the all-inclusive and the specific fitness-increasing constructs conform nicely to any attempts at a phylogenetic theory for an observed pattern of variation in a particular phenotypic feature. And yet, not all beneficial responses to environmental pressures are populational in scope nor evolutionarily significant. Short-term, non-heritable solutions to environmental challenges

are called acclimatizations. Acclimatization is "the functional compensation over a period of days to weeks in response to a complex of environmental factors, as in seasonal or climatic changes" (Folk, 1966, p. 24). Such responses occur at the level of the individual and involve changes in characteristics which are phenotypically plastic to some degree (Mazess, 1975).

Under the rubric of acclimatization are included compensatory reactions on several infra-organismal levels. Structural acclimatizations may entail anatomical, histological, or morphological accommodations. Physiological acclimatization consists of functional alterations of biochemical pathways, rates of synthesis of materials, or normal bodily processes like circulation, respiration, and excretion. Habituation is a neurologically mediated response to stress in which sensitivity to a particular stimulus is decreased over time, often following repeated exposure to the stimulus. Finally, psychobehavioral acclimatization includes sublimation, personality changes, adjustments in perception and cognition which influence behavior, and alterations in activity patterns can all be classified under this heading (Bennett, 1979; Folk, 1966; Frisancho, 1981; Mazess, 1975 [his framework used above]). Although this report will focus predominately on possible physiological acclimatizational responses, the term acclimatization will have to suffice.

Acclimatizations are, once again, individual responses to environmental stressors. Although similarities in response parameters may appear greater among individuals from the same population, experiencing the same environmental exigencies, the capabilities for such responses are common to the majority of the members of a species (Bennett, 1979; Frisancho, 1981). By means of acclimatizational mechanisms a relatively stable internal environment may be maintained in reply to the demands of a habitat without compromising function (Frisancho, 1975; Folk, 1966; Timiras, 1972). Acclimatizational responses may be considered as "part of a continuous process whereby past adaptations are modified and developed to permit the organism to function and maintain equilibrium within the environment to which it is daily exposed" (Frisancho, 1981, p. 8).

Ontogeny, Phylogeny, and Human Auxological Variation

Whether viewed as processes or results, the concepts of functional adaptation and acclimatization may be invoked to explain the bulk of observable human biological variation. Phenotypic parameters for populations as well as manifestations in individuals owe their existence to both phylogenetic and ontogenetic experiences. The evolutionary history of a population, or the genealogical history of a kindred, determines the composition

of the gene pool from which will be fabricated the genomes of individuals and the genotypes for their traits. The genetic structure of breeding groups is dependent on generation upon generation of interactions between ancestral organisms and their environments, differential morbidity, mortality, and fertility patterns, as well as the action of evolutionary forces such as mutation, drift, and migration (Bodmer & Cavalli-Sforza, 1976). Additionally, the genomic constitution of individuals is strongly influenced by mating practices of previous generations (Ayala, 1982).

Genotypically, however, organisms receive from their parents genetic information which determines the norms of reaction for the entire repertoire of phenotypic characteristics. These norms of reaction are the full range of available developmental options which can be engaged under different environmental regimes (Bennett, 1979; Dobzhansky, 1970; Futuyma, 1979). In the case of phenotypic traits displaying a simple mode of inheritance, characteristics of a qualitative nature which are either present or absent, a rather narrow norm of reaction would be indicated. Quantitative characteristics, those phenotypic traits whose expression is continuous as a function of their being influenced by many gene loci, are suggestive of a broader norm of reaction.

It is during an organism's ontogeny that the phylogenetically derived norms of reaction for various

phenotypic traits interact with each other and environmental influences while producing an adult. At any point in its development the organism is the product of these interactions. The individual responds in an acclimatizational manner, within the limits of its genetically programmed phenotypic plasticity, to a lifelong series of environmental challenges. Consequently, the phenotype is always reflective of the nature and intensity of the complex of environmental variables with which it has had to contend during development.

However, the phenotype is also reflective of the effectiveness of the organism's responses to those stressors. When the duration or intensity of the environmental stress exceeds the acclimatizational capabilities of the individual, pathology is the result. The inability of the normal compensatory mechanisms to maintain or restore the functional status quo, or to shift to a new set of equilibrium conditions, may lead to localized or generalized conditions inconsistent with normal function and development (Hill, 1971). A phenotypic variant resulting from this compromised function should not be confused with a functionally adaptive or acclimatizational adjustment.

From this discussion it should be evident that human growth and development may be viewed from both an ontogenetic and a phylogenetic perspective.

Acclimatizational and adaptational responses have been cited as bases for many inter-populational differences in growth and development (Damon, 1975; Eveleth, 1978; Eveleth & Tanner, 1976; Frisancho, 1978; Stini, 1975). Populational variation in mean body size and shape, for example, are generally accepted as being functionally related to differences in mean annual ambient habitat temperatures and the stresses they impose on thermoregulation (Gallow, Graham & Pfeiffer, 1984; Johnston et al., 1982; Roberts, 1978). Patterns of growth and development characteristic of high altitude dwellers (to be dealt with more extensively in later sections) have been hypothesized as functional adaptations and acclimatizations (e.g., Beall, 1981; Frisancho, 1969, 1981).

That human growth and development is influenced by both phylogenetic and ontogenetic factors is intuitively obvious and is not an especially astute observation, as indicated in a somewhat more general manner earlier. However, the literature acknowledging the phylogenetic contributions to and implications of auxological variation in contemporary human populations is still rather sparse; even moreso than the general theoretical work considering development and evolution (see, e.g., Goodwin, Holder & Wylie, 1983). The apparent reticence concerning the employment of evolutionary theory as a framework for more auxological investigations has been

defended by some (personal communications) with the adage: "human growth and development is too complex a process to approach in toto with simple evolutionary theory"; and explained by others, like Maynard-Smith (1983, p. 33) with: it is "because we have a clear and highly articulated theory of evolution . . . [but] no comparable theory of development." Although there is some truth to both perspectives, the explanation offered below is probably more accurate.

There may be said to exist two viewpoints or classes of auxological studies. Borrowing from sociobiology (Barash, 1982, pp. 28-29), they will be labeled proximate and ultimate auxology. From the vantage point of proximate auxology, the questions of how and why humans grow and develop as they do require the investigation of any number of a plethora of ontogenetic events and features at various levels of infra-organismal organization. Elucidation of proximate or immediate causation is the goal. This orientation characterizes the majority of auxological studies which approach growth and development as processes liable to disturbances by a host of environmental variables. Equally legitimate inquiries may be made from the perspective of ultimate auxology, which is an inherently evolutionary approach to the same general questions of how and why humans grow as they do. Such an approach considers growth and development, or some aspect

of it, as a phenotypic character and proceeds to ask such questions as: What is the evolutionary history of this character? Is this pattern of growth and development adaptively significant? These are the types of questions being asked by a few biological anthropologists (examples of whom were cited earlier) engaged in studies of functionally adaptive aspects of growth and development.

Paraphrasing Barash (1982, p. 29) again, neither approach is innately better. Both can contribute to the comprehension of biological growth and development. In fact, proximate auxological studies can identify the infra-organismal mechanisms which serve ultimate ends. In the long run, explanations of growth and development will be most satisfying when they take both perspectives into consideration.

Growth and Development

For humans, the predominant biological activity during the individual's first twenty years of life is that of growth and development (Malina, 1975, p. 1). From the proximate perspective, this is a complex activity, encompassing a variety of biological phenomena which affect a cumulative series of morphological and physiological modifications taking the organism from conception to adulthood. The transition from fertilized ovum to a fully mature adult and beyond involves both quantitative and

qualitative changes in the organism. The lexicon of auxology is replete with terms for the mechanisms by which these changes are accomplished.

The words growth and development are often incorrectly employed as synonymous, or at least functionally equivalent, concepts by persons in many diverse fields. However, in the parlance of developmental biology and auxology these two words imply two very different categories of biological activity. Growth is "a geometric process of self-multiplication of living substance, involving primarily hyperplasia (increase in cell number), hypertrophy (increase in cell size) and accretion (increase in intercellular materials)" (Malina, 1975, p. 1). In contrast, development refers to the processes by which a monocellular fertlized ovum becomes a mature, reproductively competent adult composed of somewhere between one trillion (Bonner, 1962) and 100 quadrillion (Levitan & Montagu, 1977) cells specialized into different cell types, tissues, organs, and organ systems. Developmental stages include determination, a process not yet understood, by which undifferentiated, totipotent cells are "programmed" and committed to a particular developmental fate; differentiation, the enactment of the genetic program such that the cell(s) take on observably different forms and functions; and maturation, the achievement of adult form and function (Browder, 1980). Although defined

in terms of cells, developmental constructs are readily applied to other levels of biological organization; as in sex determination of a zygote, sexual differentiation of a fetus, and sexual maturation of the adolescent.

The patterns of human growth and development, which are for the most part typically primate (Harrison et al., 1977, p. 318), are best appreciated when illustrated by standard growth curves. Two types of curves commonly used to express auxological data: the distance or cumulative curve and the velocity or incremental curve. Distance curves can be constructed by plotting consecutive observations on an individual over a specified period of time. Individual points on such curves represent the cumulative distance, in some auxological parameter, traveled by the subjects over that period of time. Velocity curves are obtained by plotting the incremental differences occurring since the last observation on some measure per unit time. Such curves indicate the rates of change over time or the velocity of growth and development. For purposes of pediatric clinical evaluation, public health screening, and population-based health and nutritional indexing, observations on the growth and development of individuals and groups are often compared to curves derived from large-scale samples of normative or standard data (Tanner, 1978c).

To better assess the growth and development of individuals related to normative standards, mean curves are supplemented by the plotting of the standard deviations from the mean or percentiles are calculated from the standard data to indicate dispersal about the median (Barden, 1979; Roche & Hamill, 1978; Tanner, 1978c). These curves "graphically portray the tremendous amount of normal individual variation within any population" (Barden, 1979, p. 427). Standard curves may be derived from data obtained in cross-sectional or longitudinal surveys. Longitudinal studies involve the repeated measurement or evaluation of individuals over many years, occasionally over the first twenty years of life. Longitudinal surveys are preferred because of the accuracy of the data collected; however, the maintenance of such long data collection periods is expensive, time-consuming, and logistically complicated (Goldstein, 1978; Marubini, 1978; Roche et al., 1981; Tanner, 1978b). To obviate such difficulties, many auxological surveys are cross-sectional in sampling methodology. Groups of individuals, representing all ages of interest, are evaluated at one time and the average values for each age class are calculated and plotted to construct the curve (Tanner, 1978b, 1978c). The applicability of cross-sectional data is limited insofar as curves derived from them are not reflective of the patterns of growth and development for the individuals

from whom the data were obtained (Barden, 1979). Cross-sectional data are valuable, however, if an object of a study is the comparison of mean rates of growth and development in different groups of individuals (Eveleth & Tanner, 1976).

The majority of the published research in auxological anthropology in which cross-sectional standards are employed focus on growth-related changes rather than developmental ones. Perhaps a function of the long-standing association between anthropology and anthropometrics and other techniques more suitable for elucidating metrical changes during ontogeny, growth has been a primary concern. Metric characters, like stature, weight, and skinfold thickness, are often very good indicators of an individual's health and nutritional status. Growth variables, when evaluated longitudinally, provide insights into an individual's relative success at dealing with past environmental insults. Research concentrating on the growth aspect of ontogeny is limited to retrospection (Tanner, 1978b, p. 78) and lacks, so far as the future growth of individuals is concerned, any general predictive applicability. Knowing, for example, than a ten-year-old female is 129 cm tall (at the 5th centile for stature) does not prove, in and of itself, too illuminating as to her final adult stature.

To make growth data more meaningful and to facilitate prediction, many clinicians and researchers include the assessment of some indicator(s) of the developmental or physiological maturity in the evaluation of their subjects. The rate at which individuals proceed from one developmental stage to another is under the influence of their own unique chronogenetic genotypes (Gedda, 1978) as well as that of certain environmental factors. As such, many individuals show a great amount of variability in terms of their stage of maturity relative to their chronological age (Barden, 1979, p. 435). From the time of conception until the achievement of adult status, growing humans, as well as their various tissues, organs, and organ systems, undergo developmental changes which occur in fairly fixed or invariant sequences. Unlike metric growth characters, developmental indicators possess "common endpoints" (Tanner et al., 1975, p. 1). There exist known minimally and maximally developed stages for certain anatomical features or physiological processes. Because of this, it is possible to determine, for example, that one individual is more skeletally mature than another her own chronological age, has less time remaining for linear growth, and is measurably closer to being an adult.

Maturity, based upon the assessment of selected developmental indicators, may be compared without employing retrospective longitudinal data acquisition methods.

The endpoints and sequences of development have been elucidated for several organ systems in humans. Developmental standards, complete with age scales and percentiles, have been constructed so that it is now practicable to evaluate and compare individuals on the bases of sexual, dental, and skeletal maturation (Barden, 1979; Tanner, 1962, 1978b). In the standard population samples the maturational indices established from these systems show positive, but relatively low, correlations with one another at a given chronological age (Marshall, 1974; Tanner, 1978b). It is generally agreed that the systems are under the influence of different genetic complexes and experience, to a great extent, separate patterns of maturation (Tanner, 1978b, p. 82). Consequently, the evaluation of development in these three systems can be an invaluable aid in the assessment of past difficulties and the prediction of future potentials in growing and developing humans.

Skeletal Development and Maturation

The analysis of osseous materials has played a prominent role in traditional as well as contemporary biological anthropology, especially in the study of fossil and prehistoric populations. Since the 1930s and the pioneering work of Todd (1930a, 1930b, 1937) and others (Sontag, Snell & Anderson, 1939), human auxologists have

also been exploiting the skeletal system for growth-related information. Of the developmental indicators of biological age, osseous maturation of the long and round bones of the human skeleton is the most commonly used (Smith, 1977, p. 19). The assessment of skeletal maturity is founded upon the observation that most bones progress through a series of developmental stages which are radiographically detectable. The stages consist of the initial appearance, relative size and shape changes, and the complete fusion of the primary and secondary centers of ossification in selected bony elements. Because the sequential series of changes from the first appearance of a bone's ossification center to its eventual fusion displays only minor inter-individual variability, while the timing of these modifications exhibit considerable variability among individuals, the achievement of a particular ossification stage assumes comparability as an indicator of developmental age (Barden, 1979; Roche, 1978).

The growth and development of the bony skeleton commences during the prenatal period. However, because of the potential risk to the rapidly developing fetus, few radiographic surveys of such young living subjects have been conducted. Therefore, although some of the information to be presented concerning skeletal development has been gleaned from studies of embryonic and fetal

systems, the discussion will be primarily applicable to the evaluation of postnatal development.

The process of bone formation, ossification, consists of the deposition of minerals within an organic matrix. Postnatal skeletal ossification is referred to as intracartilaginous or endochondral ossification as it is preceded by the production of a cartilaginous model (Francis & Martin, 1975; Roche, 1978). The majority of the human skeletal system undergoes this mode of mineralization (Barden, 1979). Typically, postnatal development of the long bones of the limbs and the short-long bones of the hands is observed predominantly in the cartilaginous centers of ends of the bones (epiphyses) as opposed to the shafts (diaphyses) (Roche, 1978, p. 321). The epiphysis remains separated from the diaphysis by a cartilage zone in which there exists a specialized area responsible for longitudinal bone growth called the epiphyseal plate. While multidirectional cartilage replacement, with respect to the primary ossification centers, occurs in the diaphysis, cartilage-producing cells (chondrocytes) adjacent to the epiphysis undergo hyperplasia followed by hypertrophy, thus expanding the plate longitudinally (Barden, 1979; Roche, 1978). Soon after, the cartilage on the diaphyseal aspect of the plate calcifies subsequent to resorption of that portion of the cartilaginous model. Linear growth continues within the epiphyseal plate so

long as the rate of chondrocytic hyperplasia on the epiphyseal aspect exceeds the pace of chrondroresorption and ossification on the diaphyseal aspect. However, chondrocyte proliferation does eventually slow, the cartilage of the epiphyseal plate is replaced by mineralized material, fusion of the diaphysis and epiphysis occurs, and linear apposition ceases (Noback et al., 1960; Roche, 1978).

The irregularly shaped, or "round" bones, like the carpals and tarsals, ossify in a manner very similar to that for the long bones. The processes are, histologically, those of endochondral ossification (Roche, 1978). Differentiated prenatally as a condensation of embryological connective tissue, the pre-round bone undergoes cavitation at the sites of future articulation and chondrification occurs (Roche, 1978). Auguring the adult bone's shape, the cartilaginous model ossifies endochondrally from one primary center (some bones have two centers) in all directions (Gardner, 1971). Irregular bones have no epiphyseal plate (except for the calcaneous (Roche, 1978, p. 325)); consequently, their final mineralized morphologies are a function of regional allometries (Roche, 1978).

Postnatal skeletal ossification is influenced, and not surprisingly, by genetic and environmental factors. Populational studies, primarily comparisons of subsaharan African and similarly descended populations

with western European and descendent groups in the United States, have suggested a genetic basis for the timing of skeletal development (Garn & Bailey, 1978, p. 318). Not only may some populations exhibit a tendency toward relatively more or less rapid skeletal maturation, as was evidenced in the black African--white European comparisons, but also differences in rate pattern throughout ontogeny have been elucidated in population surveys involving Scandinavian (Mathiasen, 1973) and Asian (Low et al., 1964; Kimura, 1972) subjects as well (see also, Eveleth & Tanner, 1976; Tanner et al., 1975). Present evidence strongly favors partial genetic control of ossification timing and epiphyseal union (Garn & Bailey, 1978).

Of course, any genetic control over skeletal maturation is hormonally mediated. The calorigenic hormones like thyroxine (thyroid hormone) regulate metabolic processes and contribute to overall growth as well as skeletal development by influencing the amount of energy available for ontogenetic activities (Barden, 1979; Lowrey, 1973; Tanner, 1978b). Somatotropin (growth hormone), which is produced by the anterior pituitary gland, exerts a profound effect on skeletal growth. By stimulating the production of the intermediary hormone somatomedin in the liver, somatotropin acts to increase mitotic activity and protein synthesis in the chondrocytes of the epiphyseal plate (Barden, 1979; Harrison et al., 1977).

While stimulating growth, somatotropin does not directly cause maturation or fusion in the skeleton. It is most likely that a hormonal mechanism is responsible for bone maturation; however, that mechanism has yet to be fully elucidated. Additionally, although the basic mechanisms are still elusive, it is clear that the actions of the majority of these regulatory molecules are highly interdependent (Barden, 1979).

Skeletal development is rather sensitive to several classes of environmental perturbation. Nutritional deficiencies have been shown to deleteriously affect skeletal maturation in many populations (Blanco et al., 1974; Frisancho, 1970, 1978). Conversely, over-nutrition has been cited as a contributor to advanced skeletal maturation in fatter children when compared to those of average weight and fatness (Frisancho, 1978; Garn & Haskell, 1960). Systemic disease experience has also been indicated to adversely affect skeletal maturation (Tanner et al., 1975). Metabolic diseases, malabsorptive syndromes, and renal disorders, as well as endocrinopathies, have all been associated with some skeletal retardation (Smith, 1977; Tanner et al., 1975). Additionally, socioeconomic status has been weakly associated with differences in ossification (Garn & Bailey, 1978); however, its effects are most probably a function of differential access to nutritional and health care resources.

Dental Development and Maturation

As is the case with the skeletal system, biological anthropologists have devoted a great amount of research effort to dental variation. For many of the same reasons as were given for the osseous skeleton, the dentition has proven to be extremely useful as a maturational indicator. There exist two approaches to the study of dental maturation which may be applied in the evaluation of both the deciduous and succedaneous dentitions in humans: the clinical method, based on emergence, and the radiographic method, based on mineralization rates and sequences (Demirjian, 1979). Clinical emergence, the initial appearance of the tooth in the oral cavity, was employed as a maturational indicator of sorts by schools and employers as early as 1837 in England (Demirjian, 1979). However, those observations were usually limited to a very few teeth, such as the second molar. The first individual to assess dental maturity based on the number of emerged teeth in the mouth was Cattell (1928). Since that time, emergence has been used to evaluate dental development in many clinical and field research situations primarily because of the ease with which it may be assessed (e.g., Brown, 1978; Filipsson, 1975; Jaswal, 1983; Moorrees & Kent, 1978). The relationships of dental emergence to sex, populational origins, nutrition, and socioeconomic status have been well researched (Bambach

et al., 1973; Johnsen, 1977; McGregor et al., 1968). The high degree of interindividual variability in timing and sequence related to these and other exogenous factors, such as crowding, infection, or premature loss of a deciduous predecessor, has caused clinical emergence to fall into disfavor as a maturational index with many authors (see Demirjian, 1979, 1978).

The radiographic assessment of dental maturation based upon the appearance and development of calcification centers for individual teeth has been shown to be a much more reliable method than those based on emergence (Demirjian, 1979, 1978; Demirjian et al., 1973). While the appraisal of clinical emergence is limited to periods from about the sixth to the thirtieth month for deciduous teeth and from approximately the sixth through the twelfth year for the succedaneous, the radiographic methods can monitor the continuous growth and development of selected teeth from birth to maturity (Demirjian, 1979). Just as with skeletal maturation, dental development begins and is potentially detectable by radiography during the prenatal period. Likewise, most auxological investigations avoid the application of X-rays at this sensitive time unless they are clinically mandated. Consequently, postnatal studies are more common.

All teeth undergo the same sequence of developmental stages during maturation; but, depending upon tooth

class, maturation is initiated at different times. There is no demonstrated overall advancement or retardation for either the teeth of the maxilla or the mandible (Demirjian et al., 1973; Demisch & Wartmann, 1956). Therefore, since a high degree of correlation has been observed for the development of the left and right dentitions (Demirjian et al., 1973; Knott & Meredith, 1966) and mandibular radiographs are more easily read than maxillary ones, the left mandibular dentition is usually considered as representative of the entire dental system (Demirjian, 1979).

The processes and events responsible for odontogenesis have been studied extensively. They include induction, differentiation, histogenesis, formation of extracellular matrix, matrix calcification, and, eventually, tooth eruption (Goose & Appleton, 1982, p. 126). Early development entails a complex series of morphogenetic movements of both mesenchymal and epithelial cells, followed by the differentiation of tooth-specific secretory cells, the odontoblasts and ameloblasts that form the organic matrices which are mineralized by dentin and enamel, respectively (Thesleff & Hurmerinta, 1981, p. 75). It is a precise pattern of mineralization in the crown and root(s) of a tooth which leads to its assumption of an adult size and shape and allows for estimations of developmental status.

Following the establishment of the crown's organic model an appositional stage of development begins, leading to enamelization of the crown by the ameloblasts (Ranly, 1979). Similar to bone ossification, enamel is formed by the incorporation of mineral salts into the organic matrix. Radiographically, this process may be seen to begin at the cuspal tips of the tooth (Demirjian, 1978; Goose & Appleton, 1982). However, before the crown is completely calcified, but following the establishment of crown morphology, the development of the roots begins (Goose & Appleton, 1982, p. 136). Just prior to the deposition of matrix near the cervical margins of the developing crown, a proliferation of cells in this region produces a structure referred to as Hertwig's root sheath which determines the number, size, and shape of the roots (Ranly, 1979). Dentinogenesis continues downward from the cervical margin, forming the roots which are subsequently covered by cementum. During its development a tooth becomes encased in an osseous crypt within the maxilla or the mandible. This crypt, through relatively uniform resorption of bone, expands to accommodate the developing tooth until root formation begins (Goose & Appleton, 1982, p. 137). With the development of the roots the tooth usually begins to migrate occlusally to assume a functional position. The tooth is classified as mature when crown calcification is complete and the

root apex is closed (Demirjian, 1978; Goose & Appleton, 1982).

Dental growth and development, including formation, apical closure, adult morphology, and emergence, is generally agreed to be under a strong genetic influence (Garn & Bailey, 1978; Goose & Appleton, 1982). That the development of the human dentition is highly heritable has been supported by numerous populational and family-line comparisons conducted over a substantial period of time (Biggerstaff, 1979; Garn & Bailey, 1978). Studies on Aleuts (Garn & Moorrees, 1951), comparisons of individuals of African and European descent (Garn et al., 1973a), and investigations of sex differences in dental maturation (Garn et al., 1958; Infante, 1974) have all indicated the existence of a significant genetic component. Opposite sex, same sex, dizygotic, and monozygotic sibling studies have yielded "correlations of the expected order of magnitude" for a highly heritable complex of characteristics like those found in dental maturation (Garn & Bailey, 1978, p. 317). Additionally, theoretical, in vivo nonhuman subjects studies, and in vitro experimentation consistent with the clonal model of tooth differentiation (Osborne, 1978) also support a predominantly internal mechanism controlling dental differentiation (Goose & Appleton, 1982; Glasstone, 1952).

Much of the certainty expressed in the literature concerning the degree of genotypic influence on dental maturation is directly related to the common observation of tremendous developmental stability in response to environmental challenges (Biggerstaff, 1979; Demirjian, 1978). The effects of undernutrition on the permanent dentition's development (not clinical emergence) is detectable in the more extreme cases but far less than for skeletal development; the same is true for overnutritional extremes evidenced by obesity (Garn & Bailey, 1978; Garn et al., 1965). As was noted earlier, a very small socioeconomic effect has been demonstrated for emergence; however, that is not the case for calcification (Demirjian, 1978; Garn et al., 1973b).

The effects of many systemic diseases on dental maturation is generally viewed as minor to negligible (Demirjian, 1978). Those insults which are registered are not responded to in the manner or degree as with other somatic systems. Studies of the dental development in juveniles afflicted by serious endocrinopathies which severely retard general growth and development indicate a very mild dental manifestation (Demirjian, 1978). However, in Wagner's (1963) investigation of dental responses to adrenocortical hyperplasia, androgenic virilism, or sexual precocity, advanced development was noted. Yet in a study of drug-induced pseudohypoparathyroidism, which

drastically affects calcium biochemistry, Robinson, Harris, and Harvey (1983) report no significant delay in dental maturation (calcification) although observing significant disturbance in emergence and skeletal maturation. Perhaps more investigations of dental development's association with hormones would be illuminating. Demirjian (1978, p. 419) cites the professional distinction between clinical endocrinology and dentistry as an impediment to this, however.

Sexual Development and Maturation

The postnatal period of greatest sexual development, differentiation, and maturation in humans is commonly referred to as puberty. Derived from the Latin pubescere (to become hairy), puberty is perhaps one of more intensively and extensively studied stages of growth and development as it may be found discussed in anthropological, auxological, clinical, genetic, psychological, physiological, and sociological literature (Brooks-Gunn & Petersen, 1983). From an auxological perspective, sexual development is predominantly a complex series of overlapping biological modifications by which the juvenile human is metamorphosed, so to speak, into a reproductively capable adult. There are changes in nearly all structures and organ systems of the body (Marshall, 1978a). They do not all commence at the same age, nor take the same

amount of time in all individuals; neither is the order in which different structures begin their pubertal maturation in different individuals the same (Marshall, 1974; Tanner, 1978b). However, the sequence of events in the pubertal maturation of each of the anatomical structures and organ systems is invariant, facilitating the construction of standards of development (Marshall, 1978a; Tanner et al., 1975). Although the changes which occur may involve various hierarchical levels (e.g., biochemical, cellular, histological, etc.), the more useful auxological standards focus on maturational indicators which are external and may be readily evaluated by either visual inspection or palpation (Tanner, 1978b). The more common features evaluated include the distribution of axillary and pubic hair in females and males; breast development and menarche in females; and genital maturation and testicular volume in males (Tanner, 1962, 1978; Van Wieringen et al., 1971).

Females

Female humans exhibit a great deal of variability in the initiation and timing of pubertal events; most of which are preceded by a relatively sharp increase in growth velocity, the adolescent growth spurt. However, prior to the onset of the more easily recognized developments of sexual maturation, changes involving primary and

accessory sexual organs begin. Between 8 and 10 years the pelvis begins to assume the adult female contour (Lowrey, 1973). As the volume of the pelvic cavity increases, the bilateral ovaries, fallopian tubes, and uterus situate themselves relatively nearer the pelvic floor (Marshall, 1978a). During this time the ovaries nearly double in size, fallopian tube diameters increase accompanied by the establishment of ciliated epithelium, and the uterine corpus surpasses the cervix in size (it was one-half the cervical length at birth) attaining secretory and proliferative functions (Lowrey, 1973; Marshall, 1978a; Tanner, 1962). Vaginal modifications also mark the early, almost covert, stages of puberty. A 50 percent increase in size usually occurs between 10 and 12 years of age, while cytological changes in the vaginal epithelium, the first unambiguous signal of the initiation of puberty, occur (Marshall, 1978a). Additionally at this time (8-12 years), the mons pubis and labia majora assume adult proportions as a result of differential fat deposition (Marshall, 1978a).

Usually the first event in female sexual maturation to be noticed is the development of the breast to the bud stage (Tanner, 1978b). The elevation of the breast and the papilla forming a small mound characterizes the bud stage, along with a minor increase in areolar diameter (Tanner, 1962; Marshall, 1978a). The age range

for the initiation of the breast bud is from 9 to 13 years in European and American females of European descent (Tanner, 1978b). Subsequent breast development includes increases in the diameter, absolute and relative, of the areola and the assumption of a continuously rounded contour. By menarche, most females' breasts have increased in size to various degrees but nearly all are characterized by enlarged papillae and areolae which form secondary mounds projecting above the bodies of the breasts (Marshall, 1978a). The final adult stage of breast development is attained with the disappearance of the secondary elevation. This last stage is indeed quite variable, with a majority of females entering it during adolescence and some not attaining it until the first pregnancy and later (Marshall, 1978a). Development from juvenile to adult breast status takes, on average, 4 years to complete; although some experience this in 1.5 and some take more than 5 years (Tanner, 1978b, p. 67).

In two-thirds of European and American females the initial appearance of pubic hair occurs just after the breast bud (Tanner, 1978b, p. 65). Minimal growth about the labia first appears between 9.5 and 13 years, with a median age of 11.3 years (Marshall & Tanner, 1969; Van Wieringen et al., 1971). This hair is usually lightly or nonpigmented. As the female develops, the pubic hair becomes more visibly pigmented and adult in type while

distributing itself centrally and superiorly. The lateral spreading of pigmented, adult-type pubic hair indicates the achievement of adult status (Van Wieringen et al., 1971). The adult distribution is usually reached between 12 and 17 years in females (Marshall, 1978a, p. 162). Axillary hair, however, makes its first appearance a bit later around 12 to 14 years of age and continues to increase in amount until early adulthood (Lowrey, 1973).

Menarche occurs rather late in sexual maturation, with the average ages for females in Europe and of European descent in North America being between 12.7 and 13.2 years (Barden, 1979; Lowrey, 1973; Tanner, 1978b). One of the better studied indicators of female pubertal development, menarche has been determined to occur between 11 and 15 years in most populations of the world (Marshall, 1978a; Tanner, 1978b). The age at menarche displays considerable independence from the other characteristics, such as breast and pubic hair development; however, it does show a close relationship with the adolescent growth spurt, occurring on the average one year after the attainment of peak height velocity (Barden, 1979; Daniel, 1983). It should be noted that although menarche represents a definitive stage in sexual maturation, it does not necessarily imply mature reproductive capabilities for the newly mensturuating female (Tanner, 1978b, p. 66).

Males

Male sexual development and maturation, although usually beginning later, is no less variable than that for human females. As with females, sexual maturation begins with changes affecting the primary and accessory sex organs; but, unlike the female situation, this development is more easily observed and measured. An increase in testicular volume begins between 9.5 and 13.5 years of age (Marshall & Tanner, 1970) and signals the initiation of puberty. In a four-year maturational period testicular volume will increase from a prepubertal 1 to 3 ml to an adult range of 12 to 25 ml when measured by the Prader orchidemeter (Marshall, 1978a, p. 150). There is a tendency among earlier maturers to achieve greater testicular volulmes than males who begin puberty at a later age (Marshall, 1978a, p. 150; Zachmann et al., 1974). Pubertal growth in testes is accompanied by the histological maturation of the seminiferous tubules, differentiation of the Leydig cells, and establishment of the germinal epithelium (Marshall, 1978a). Additionally, the seminal vesicals, epididymis, and prostate gland exhibit rapid enlargement concomitant to that of the testes (Goss, 1978; Marshall, 1978a). Although the development of these latter structures is difficult to assess in subjects, testicular volumetric increases may be evaluated by visual inspection and/or palpation of the externally

situated scrotum (Tanner, 1962, 1978b; Van Wieringen et al., 1971).

Sexual maturation of the penis initiates usually within a year following the first evidence of testicular enlargement (Marshall & Tanner, 1970). Accelerated penis growth begins on average at age 12.5 years and ends with the attainment of adult size about two years later (Tanner, 1978b, p. 61). Penile maturation entails textural and pigmental changes as well as enlargement. Most auxological investigations of male puberty examine scrotal development along with that of the penis, assessing maturational progress for the external genitalia. The scrotum enlarges relative to the juvenile penis as a function of increasing testicular volume. This is accompanied by a reddening of the scrotal skin. Penile enlargement in length and diameter occurs and elaboration of the glans occurs. By the time the external genitalia have attained adult dimensions, they have also become significantly darker (Tanner, 1962; Van Wieringen et al., 1971).

The initial appearance of male pubic hair occurs near the base of the penis. It is at first lightly pigmented and only slightly curled. Its development mirrors that for females in terms of the patterns of increased pigmentation, coarseness, and distributional changes (Marshall, 1978a). In males of European descent pubic hair growth may begin as early as 10.5 years, while the

fiftieth centile is near 12 years of age (Marshall & Tanner, 1970; Van Wieringen et al., 1971). The final adolescent pubic hair status is reached, quite variably, sometime between 15 and 18 years of age; however, fully adult distributions are usually not attained until the middle of the third decade of life (Marshall, 1978a, p. 155).

Generally, the development of axillary and facial hair in males is not begun until the individual is well into puberty (Marshall, 1978a). Axillary hair is first observed about two years after the initial appearance of the pubic hair and when the external genitalia are nearly adult (Tanner, 1978b). Although facial hair in males may appear almost simultaneously with axillary hair, it normally succeeds it over a year; appearing first at the corners of the mouth, then on the upper lip, cheeks, and chin during the next two to three years (Marshall, 1978a). Facial hair rarely appears on the chin prior to the completion of male genital and pubic development (Marshall, 1978a; Tanner, 1962). Standards for axillary and facial hair development are not yet available as very little in the way of precise research has been done on this subject (see, e.g., Lunde, 1984; Neyzi et al., 1975a, 1975b; Thomas & Ferriman, 1957).

Insofar as maturation of the different sexual indicators is relatively independent, the puberty of

females and males is quite similar. For example, female breast and pubic hair development is not simultaneous. In fact, the majority of developing females are well into breast development prior to the first appearance of pubic hair. The same is true for female axillary hair; however, some females do develop axillary hair before either breast or public hair development ensues (Marshall & Tanner, 1970; Marshall, 1978a; Tanner, 1978b). Menarche usually occurs late in sexual maturation and some females do not experience it until all other sexual development is complete. In the great majority of cases, though, female pubertal development begins after the attainment of peak height velocity (Marshall, 1978a; Tanner, 1962, 1978b).

Similarly, male pubic hair and genital development are not synchronous. Normally, as indicated earlier, sexual maturation of the external genitalia precedes the appearance of pubic hair somewhat. Yet, the stage of genital development during which the growth of pubic hair begins is quite variable. It is, notes Marshall (1978a, p. 157), "entirely normal for the genitalia to reach [adult status] before there is any growth of hair . . . [while] pubic hair growth without genital development is very unusual." Males are very dissimilar to females in terms of the relationship between the initiation of puberty and the growth spurt. Their peak height velocity

occurs after the genitalia begin to mature (Marshall & Tanner, 1970).

Information concerning the degree of genetic influence on sexual maturation is generally sparse. This is especially true for male pubertal development. Family line, populational, and gender differences are suggestive, yet much more research is required (Garn & Bailey, 1978). For females, age at menarche has proven a most profitable variable for investigation of genetic contributions. Family studies examining the sons and daughters of early and late maturing females, sibling, and dizygotic and monozygotic twin comparisons have all pointed to very real, and significant, correlations (Garn & Bailey, 1978; Marshall, 1978a). Age at menarche has a discernable genetic component whose effect has been observed in the sexual development of progeny of both sexes, suggesting sex-linkage but not sex limitation (Garn & Bailey, 1978, p. 326).

Any genetic influence on sexual maturation is most likely manifested in hormonal control mechanisms. The role of hormones in the development of sexual characteristics is well documented (Cutler et al., 1983; Daughaday, 1981; Smith, 1977; Winter, 1978). Female sexual maturation is influenced primarily by the estrogens, which are responsible in great part for the development of the breasts, uterus, vagina, and portions of the pelvis

(Tanner, 1978b; Winter, 1978). Adrenal androgens are presumed to control pubic and axillary hair growth in females (Tanner, 1978b). Small pubertal prolactin secretions may be responsible for advanced female breast development by facilitating the elimination of the areolar secondary mound (Tanner, 1978b). Additionally the gonadotropins and progesterone are involved in uterine and ovarian development during adolescence (Winter, 1978). In males, testosterone, secreted by the testicular Leydig cells, is responsible for pubertal development of the penis, prostate gland, seminal vesicles, and pubic, axillary, and facial hair (Tanner, 1978b). Timing lags between the testosterone-mediated initiation of puberty and, for example, the appearance of facial hair are suggested to result from a sequential maturation of testosterone receptors (O'Mally & Schrader, 1976; Tanner, 1978b). The gonadotropins, when secreted in males, are responsible for the growth of the seminiferous tubules and the stimulation of testosterone production. Other gonadotropin-related changes, especially in adolescent male sexual behavior, are only now being explored (Tanner, 1978b; Winter, 1978).

Just as well-researched as the hormonal influences on sexual maturation are those of environmental variables, such as nutrition and disease. Nutritional perturbation is paramount. The timing of sexual developmental events

has been shown to be as much as four years delayed when lean and obese females are compared (Garn & Haskell, 1960). In malnourished populations and groups from lower socioeconomic strata, females experienced delayed menarche compared to nutrionally well-off individuals (Eveleth & Tanner, 1976; Frisancho, 1978). Undernutrition delays the onset of puberty in males as well (Frisch & Revelle, 1969; Tanner, 1962). Directly related to nutritional influences on the age of menarche is the work of individuals like Frisch (1972, 1975) and others (Frisch & McArthur, 1974; Frisch & Revelle, 1970, 1971) who have hypothesized the hotly debated critical fat and critical body weight associations with menarche and menstruation (Billewicz et al., 1976; Cameron, 1976). Malcolm's review of the effects of protein-energy malnutrition also concludes that sexual maturation in both sexes can be markedly delayed by malnutrition (1978, p. 367). Disease experience, especially malabsorption syndromes and chronic infections, have been shown to delay sexual maturation in both sexes (Tanner, 1978b; Smith, 1977). Extreme psychosocial stress and emotional deprivation have been cited for retarded metric growth and suggested for developmental delays at puberty in some cases (Gardner, 1972; Tanner, 1978b). And, recently, clinicians and researchers have become interested in the delays in female development related

to physical activity levels (Frisch, 1983; Frisch et al., 1981).

Relationships between the Different Developmental Indicators

The relationships among dental, skeletal, and sexual maturational indices have been examined extensively (e.g., Lacy, 1973; Lewis & Garn, 1960; Marshall, 1978b; Steel, 1965). Contrary to long-held beliefs (see Demirjian, 1979, p. 96), dental and skeletal maturity are not closely related. When emergence is considered, pre-pubertal individuals who are skeletally advanced do have a greater number of teeth in occlusion on average than those who are skeletally delayed (Demirjian, 1979; Tanner, 1978b). However, when dental maturity is examined radiographically, a weak correlation becomes weaker (Demirjian, 1978). The correlation between skeletal age and dental age at a given chronological age has been found to be approximately 0.4 (Tanner, 1978b, p. 82). This is interpreted as indicating the influence of some "overall general factor of maturity" on two biological systems representing separate maturational pathways (Tanner, 1978b, p. 82). The relationship between pubertal maturational parameters and dental development are equally weak (Demirjian, 1979). These same degrees of relatedness obtain in studies of children afflicted with various hormonal or systemic disorders (see, e.g., Edler, 1977;

Myllarniemi, Lenko & Perheentupa, 1978; Robinson, Harris & Harvey, 1983; Sears, 1979). In addition to their relative independence of dental maturation, skeletal and sexual maturation are both less stable in the face of environmental insults than dental development.

Skeletal maturity does appear to be related to some pubertal indicators. Age at menarche in females, although not so closely related as it was once believed, shows a closer relationship with skeletal age than chronological age (Marshall, 1978b); however, "closer" should not necessarily be equated with "strong." The correspondence between skeletal maturation and other indicators, such as male genital development and female breast development, is even more tentative in healthy individuals. But, in individuals experiencing nutritional and/or disease stress, both sexual maturation and skeletal development exhibit similar degrees of delay (Frisancho, 1978).

Growth Disorders/Disorders and Growth and Development

As assessed by standard growth metrics or the developmental indicators of dental, sexual, and skeletal maturation, human ontogenetic progress may be influenced by both genetic and environmental factors. For the pediatrician or clinical auxologist, discerning the etiology of a delay in growth and/or development is no mean task as there exist several hundred different clinically

recognized disorders in which growth deficiency or developmental delay is a prominent feature (Smith, 1977, 1976). Generally, even in the absence of other clinical manifestations, statural or weight deficiences, determined by comparison to populational standards, are the first indications of a possible auxological problem. Further investigation by the clinician usually identifies this deficiency as the product of a recognized growth disorder or as a developmental delay resulting from compromised function associated with a particular disease. Following an outline by Tanner (1978b, p. 206), a brief review should distinguish these possibilities.

Delays in growth and development have many possible etiologies; not the least of which are genetic ones. An individual in whom statural or developmental delay is presented (usually below the third centile for age) when compared to populational standards may be growing quite normally in terms of the inherited developmental program. A review of family histories should tend to uncover whether this is true. The existence of similar patterns in siblings, parents, or other relatives would support a familial delay by hypothesis (Lacey & Parkin, 1974). However, in the case of many chromosomal anomalies, the pattern of growth and development, although inherited, may not be considered normal as it is a pathological result of compromised function. Well-known examples of

cytogenetic aberrations which affect growth and development are trisomy 21, Turner's (45,X) syndrome, trisomy 18, and XXY syndrome (Brook et al., 1974; Ratcliffe et al., 1982; Smith, 1977). Growth-related symptoms range from slighly delayed skeletal maturation and no pubertal development in Turner's syndrome females, to rapid skeletal growth with poor genital maturation in XXY males Ratcliffe et al., 1982; Tanner, 1978b).

Many instances of developmental delay are congenital and of prenatal onset. Manifested at birth in small for gestational age neonates, prenatal onset growth deficiency may often result in poor growth and developmental delay long into ontogeny (Smith, 1977). Uterine crowding, in the case of twins or triplets, maternal malnutrition, hypertension, toxemia, renal disease, heart disease, and drug use may all lead to compromised fetal development which may have postnatal implications, such as those in the Silver-Russell syndrome (Buckler & Robinson, 1974; Smith, 1977; Tanner, 1978b; Tanner, Lejarraga & Cameron, 1975). Additionally, maternal infectious disease experiences may negatively influence prenatal and subsequent development. These include rubella, toxoplasmosis, cytomegalic inclusion disease, and syphilis (Smith, 1977, p. 83).

Perhaps the most thoroughly studied disorders in which altered patterns of growth and development are

primary manifestations are those involving the endocrine system. Deficiencies in somatotropin and thyroxine, or in their releasing factors, have long been associated with poor growth and development (Daughaday, 1981; Smith, 1977). Although an hereditary predisposition for somatotropin inadequacy is postulated, most cases are classified as idiopathic (Smith, 1977; Tanner, 1978b). Similarly, the genetic component of hypothyroidism is unknown. More common in females (79 percent), thyroxine deficiency is usually secondary to partial or complete absence of the thyroid gland and less commonly due to a defect in thyroxine biosynthesis (Smith, 1977, p. 97). The third major class of endocrine disorders which influence growth and development involves the adrenal glands, often in association with other glands. The results of adrenal malfunction can be rapid sexual maturation, precocious puberty, leading to tall for age, and advanced for age skeletal development but also to early maturation and short adult stature (Tanner, 1978b).

If endocrinopathies are the better known of the internal environmental causes of dysontogeny, then nutrionally-related disorders are their external environmental counterparts. Protein-energy malnutrition (Malcolm, 1978; Viteri & Torun, 1980), hypercalcemia, hypokalemia, and other dietary deficiencies in fats, vitamins, and minerals can all deleteriously affect growth

and development (Baker, Frank & Hutner, 1980; Bergmann & Bergmann, 1978; Goodhart, 1980; Jelliffe & Jelliffe, 1978). In addition to inadequate nutritient resource access or intake, which are often mediated by socioeconomic conditions and dietary behaviors, malabsorption syndromes are prominent as causes of malnutrition, starvation, and retarded growth and development (Fein, 1980; Frisancho, 1978). One of the more common malabsorption syndromes to affect growth and development is celiac disease. Due to an anomalous reaction to glutens in foodstuffs, celiac disease produces individuals whose usual response is simply short stature (Tanner, 1978b). However, other disorders associated with flat jejunal mucosa and leading to secondary celiac disease are diabetes mellitus, infectious hepatitis, pancreatic disease, kwashiorkor, etc. (Broitman & Zamcheck, 1980). The effects on growth and development of any of the malabsorption syndromes depend upon the extent, severity, and type of nutritional inadequacy caused. In many instances these syndromes are secondary to infectious disorders and/or complications of antibiotic therapeutic measures, especially for chronic infections and disorders.

An area of relatively new and increasing interest to auxologists, both clinical and anthropological, is the effect of chronic, general diseases on human growth and development. For reasons which are not entirely clear,

cardiac defects, hepatic disease, renal insufficiency, and disorders entailing respiratory obstruction have been associated with retarded growth and development as evaluated by metric and maturational standards (Lowrey, 1973; Smith, 1977; Tanner, 1962, 1978b). Such observations have inspired inquiries into patterns of growth and development associated with other chronic disorders such as thalassemia (Laor, Garfunkel & Koyoumundjisky-Kaye, 1982; Weatherall, 1967), asthma (Hauspie, Susanne & Alexander, 1976), sickle cell disease (McCormack et al., 1976; Aschcroft, Sergeant & Desai, 1972), and epilepsy (Robinson, Harris & Harvey, 1983). Interest in such studies has been stimulated by clinical and auxological concerns; desires to corroborate clinical observations, to construct a clinical taxonomy, to more fully comprehend a chronic disease's progression, and to see how humans grow, are among them.

It is estimated that in the United States between 10 and 20 percent of individuals 17 years old and younger are afflicted with some chronic disorder (Jennison, 1976; Pless & Roghmann, 1971). The most frequent chronic conditions of early and middle childhood include asthma, cerebral plasy, diabetes mellitus, epilepsy, and orthopedic problems; and of middle childhood and adolescence are chronic renal failure, collagen vascular disease, gastrointestinal inflammatory disease, essential

hypertension, and various neoplasias (Smith, 1983, p. xv). The effects of one syndrome, the most frequent inherited chronic lethal disorder among growing individuals in the United States and Europe, cystic fibrosis, are often manifested throughout the postnatal growth period. Observations on this illness, which includes endocrinological, gastrointestinal, and pulmonary complications, have included delayed growth and sexual maturation in both females and males.

Cystic Fibrosis

General

Although references made in the old German folklore (Wood, Boat & Doershuk, 1976, p. 834) and clinical observations made as early as 1913 (Garrod & Hurtley) and 1924 (Clarke & Hadfield) were consistent with its diagnosis, cystic fibrosis of the pancreas (CF, mucoviscidosis, fibrocystic disease of the pancreas) was initially recognized as a distinctive clinical entity in 1936 (Fanconi, Uehlinger & Knauer) and was well established in the medical literature two years later (Andersen, 1938; Blackfan & May, 1938; Harper, 1938). CF, commonly referred to as the most frequent inherited fatal disorder among Caucasian populations in the United States and Europe, is characterized by generalized exocrine gland dysfunction and chronic involvement of the

gastrointestinal and respiratory systems (Harris & Nadler, 1983; Wood, Boat & Doershuk, 1976). Additionally, CF is characterized by abnormally elevated sweat electrolytes (DiSant'Agnese & Farrell, 1976). Until recently, CF was considered to be nearly always fatal in infancy and early childhood (Shwachman, Kulczycki & Khaw, 1965; Shwachman & Kulczycki, 1958). Such a view is inaccurate now and probably could be attributed to previous misdiagnoses by physicians unfamiliar with the disorder, and lack of effective detection or therapeutic technologies (Frydman, 1979, p. 211). However, 46 years after the general recognition of CF, the basic biochemical or structural anomalies responsible for the disorder, as well as the range of phenotypic and genotypic variability associated with the syndrome have yet to be elucidated (Frydman, 1979; Harris & Nadler, 1983; Wood, Boat & Doershuk, 1976).

Epidemiologic and Genetic Aspects

The success of efforts to estimate the epidemiological parameters of incidence and prevalence for CF has been typified as "necessarily minimal" (Wood, Boat & Doershuk, 1976, p. 835) and fraught with "ignorance and confusion" (Frydman, 1979) on the part of researchers. Several reasons have been advanced to account for the problems with these estimates: (1) the most competent diagnostic efforts often fail to detect CF in all those

who die in infancy or early childhood (Wood, Boat & Doershuk, 1976, p. 835); (2) the fairly recent description of CF as a specific disease entity; (3) the recent observations concerning the apparently wide range of clinical manifestations and different degrees of severity in CF; and (4) the difficulty, given laboratory screening technologies, in establishing firm diagnoses in the past (Frydman, 1979, p. 211). Most researchers have felt confident, however, with observations indicating the highest incidence for the disorder to be in caucasian populations from middle and western European countries and their descendents (Harris & Nadler, 1983; Klinger, 1983; Steinberg & Brown, 1960; Wright & Morton, 1968).

Based on the assumption of a recessive mode of inheritance, the CF homozygote live birth rate is estimated at approximately 1 in 2,000 for Caucasians in the United States (Harris & Nadler, 1983). This is a generally accepted figure as the reported incidence of CF live births in the United States has ranged from 1 in 100-500 to 1 in 8,000-83,000 (Warwick, 1978). The more frequent and conservative estimates of 1 in 3,700 (Steinberg & Brown, 1960), 1 in 2,400 (Kram et al., 1962), 1 in 2,500 (Sultz et al., 1966), and 1 in 1,900 (Merritt et al., 1962) still makes CF the most common of any lethal/sublethal autosomal recessive disease in Caucasians (Klinger, 1983). Employing the conservative figures for

homozygote incidence, the frequency of heterozygotes should approximate 0.05 in these populations (Harris & Nadler, 1983). Although the highest known frequencies have been reported for the European Caucasians and their descendents, CF is by no means exclusive to them.

CF has been diagnosed in nearly all geographic populations and ethnic groups (Harris & Nadler, 1983). In Americans of subsaharan African descent the incidence of CF live births has been estimated at 1 in 17,000 (Kulczycki & Schauf, 1974). The study of Wright and Morton (1968) yielded an estimate of approximately 1 in 90,000 for Americans of East Asian descent in Hawaii. Additionally, cases of cystic fibrosis have been documented for Amerindian (Harris & Riley, 1968), African (MacDougall, 1962), Japanese (Ikai et al., 1965), Indian (Reddy et al., 1969), and Israeli Ashkenazem (Levin, 1963) populations.

The observed patterns of inheritance strongly suggest that CF is transmitted as an autosomal recessive allele and this view is now the majority opinion. The evidence favoring the autosomal recessive model includes (1) equal numbers of afflicted females and males, (2) perfect concordance in monozygotic twins, and (3) expected incidence values for autosomal recessive trait, in siblings and relatives of index cases, were approached (Danks, Allan & Anderson, 1965; Harris & Nadler, 1983;

Lave, May & Reed, 1949; Merritt et al., 1962). Also, the observations of Cohen (1975) and Grand et al. (1966) of the frequency of normal births to CF females and the frequency of affected births to obligate heterozygotes marrying for a second time (Harris & Nadler, 1983) approximated predicted frequencies under an autosomal recessive model. Further support for this argument comes from an examination of the Vatican's records of dispensations for cousin-cousin marriages which were reported to be consistent with an autosomal recessive CF allele (Nature, 1981).

Although generally accepted, this model has not met with universal agreement (Frydman, 1979; Harris & Nadler, 1983). Simple autosomal dominance has been suggested by several authors (Bauman, 1958; Koch et al., 1960) and subsequently rejected following critiques of their calculations and analytical methods (Frydman, 1979). Roberts (1960) concluded, based on the observed proportion of CF cases for 73 families, that recessive inheritance was untenable. His analytical techniques were also challenged (Steinberg & Brown, 1960).

While a simple autosomal dominant alternative is no longer seriously considered, there are still researchers who do not believe that the autosomal recessive model fits the incidence or the apparent phenotypic heterogeneity. Based on studies of metachromasia in CF and normal fibroblasts, Bearn (1973a) proposed a two-locus

homozygous recessive inheritance. Schapp and Cohen (1976) offered a two-locus dominant hypothesis to explain occasions of abnormally high incidence within families. Most recently, Danks et al. (1983) also concluded that CF incidence in first cousin data could be better accounted for by inheritance at two loci. The evidence for all these options is still tentative. Consequently, most researchers and clinicians will assume the single-locus autosomal recessive model until future research should falsify it (Harris & Nadler, 1983, p. 2).

The assumption of this model places the relative frequency of the CF allele at approximately 0.02 (Harris & Nadler, 1983). Such a high relative frequency for a deleterious allele is not readily explicable by mutation rate alone (Bearn, 1973b; Knudson, Wayne & Hallett, 1967). Therefore, several evolutionary mechanisms have been postulated to account for the gene frequency in Caucasians. Prominent among the theories have been several arguments for natural selection and heterozygote advantage (Knudson, 1979; Livingstone, 1980). Stuart and Burdon (1974) have suggested a selective resistance to typhus bacteria Proteus OX19; Crawford (1975) proposed a tuberculosis-CF association; and Super and Schalkwyk (1979) have tested CF heterozygote resistance to malaria. To date no conclusive evidence has been reported for these associations. Perhaps a more productive series of studies are

those dealing with increased heterozygote fertility. Hallett, Knudson, and Massey (1965), Knudson, Wayne, and Hallett (1967), and others (Bearn, 1973a; Danks, Allan & Anderson, 1965) have reported a possible heterozygote reproductive advantage in CF parents and grandparents of a magnitude great enough to account for the high relative gene frequency. Pritchard, Hickman, and Nelson (1968) noted an increased fertility in male CF heterozygotes and an excess of male progeny for these individuals. Recently, a population genetics model for CF in the United States was advanced incorporating the possible selective advantage for heterozygotes (Beck, 1982). In addition to selection, genetic drift, more specifically founder effect, has been proposed to explain several cases of exceptionally high incidence among populations of Brittany (Bois et al., 1978), South Africa (Super, 1978), and northern Ohio (Amish) (Klinger, 1983). Relative isolation and supposed inbreeding in these groups is thought to make genetic drift a likely candidate to maintain reported incidence levels. As with the selection arguments, conclusive evidence has yet to be elucidated and all theories are tentative.

Attempts at establishing linkage relationships with other genetic loci, such as those for the ABH (Virtanen, 1966), MNS (Steinberg & Morton, 1956), and HLA systems (Gotz, Ludwig & Polymenidis, 1974) have so far

been unsuccessful. The chromosomal location of the CF gene(s) is unknown (Rosenstein, Langbaum & Metz, 1982) and the chromosomal complement of the CF patient is normal (DiSant'Agnese & Davis (1976). The coincidence of CF with a number of other inherited disorders is "probably attributable to chance alone" (Rosenstein, Langbaum & Metz, 1982, p. 113).

Pathophysiological Aspects, General

Research into the basic defect(s) responsible for CF have done little to settle questions concerning the genetics of the disorder. CF is not so much a disease as it is a collection of symptoms, a syndrome, with a variety of expressions (Wood, Boat & Doershuk, 1976). As such, the distinctions between primary and secondary consequences of the pathology in CF are often blurry at best. Adding to this difficulty are the perceptions of phenotypic and clinical variability in such features as organ system involvement, symptom severity, and age at diagnosis (Barbero, 1982; Bonforte, 1978; Scully et al., 1977). Such observations have been predominantly anecdotal; however, recent studies have apparently identified qualitatively different phenotypic classes of CF (e.g., Sing et al., 1982). Although the degree of involvement may indeed vary among many individuals, CF can be modally characterized by generalized defects of exocrine glands

which present with gastrointestinal complications and progressive pulmonary involvement.

Exocrine System Involvement and Diagnosis

The overwhelming majority of CF patients experience obstruction of exocrine gland ducts, or the conduits for their secretions, in the lungs, paranasal sinuses, salivary glands, duodenum, pancreas, biliary system, and uterine cervix (Wood, Boat & Doershuk, 1976, p. 837). Compared with the exocrine secretions of nonafflicted individuals, those of CF subjects are typically more inspissated, or viscous. This increased viscosity has been causatively associated with the systemic obstructions and has been variously attributed to relative dehydration, increased electrolyte concentrations, and abnormal concentrations of organic materials (DiSant'Agnese & Farrell, 1976; Schmidt, Abiodum & Tolckmitt, 1981; Wood, Boat & Doershuk, 1976). Of these suggestions, firm experimental support exists for increased organic solute concentration and elevated electrolytes, especially sodium, chloride, and calcium ions (DiSant'Agnese & Talamo, 1967; Schmidt, Abiodum & Tolckmitt, 1981; Wiesmann, Boat & DiSant'Agnese, 1972; Wood, Boat & Doershuk, 1976).

The abnormally high concentrations of sodium and chloride ions in the sweat and other serous secretions of individuals with CF have proven to be the basis for

positive diagnosis and ascertainment of this syndrome. Focusing on chloride levels primarily, an individual is said to have tested positively for CF if values (for chloride) of greater than or equal to 60 mEq per liter are obtained (Wood, Boat & Doershuk, 1976). Diagnoses are rarely based upon sweat tests alone and positive sweat tests, if not corroborated by clinical observations of CF (family history, pancreatic insufficiency, and/or pulmonary disease), may be due to laboratory error, edema, or other conditions such as G6PD deficiency and malnutrition (Harris & Cohen, 1963; Lobeck, 1972; Wood, Boat & Doershuk, 1976). Reports of significant heterogeneity in sweat-chloride values among CF patients have stimulated research and debate concerning both diagnostic and prognostic implications of the test (Corkey et al., 1983).

Gastrointestinal System Involvement and Nutrition

Gastrointestinal complications often present during infancy as the initial indication of CF (DiSant'Agnese & Farrell, 1976). Seven to 25 percent of CF neonates exhibit gastrointestinal obstruction in the form of meconium ileus (Wood, Boat & Doershuk, 1976, p. 846). Medical or surgical reduction is indicated and those individuals surviving the procedure are usually given a prognosis similar to that for other CF patients (Lloyd-Still, 1983a).

Perhaps the most consistent gastrointestinal manifestations of CF are maldigestion and malabsorption of nutrients secondary to pancreatic insufficiency. Approximately 85 percent of diagnosed CF patients evidence this malady to some degree (Chase, Long & Lavin, 1979). Those so afflicted generally present with frequent loose fatty stools (steatorrhea), excess flatulence, and failure to gain weight (Wood, Boat & Doershuk, 1976, p. 846). Nutritional deficiencies in proteins, fats, vitamins, and minerals have been documented for CF subjects. Consequently, pancreatic enzyme and nutrient supplementation therapies are regularly employed.

One of the predominant exocrine pancreatic deficiencies is in the class of enzymes involved in protein and peptide hydrolysis including trypsin, chymotrypsin, and the carboxypeptidases (Chase, Long & Lavin, 1979, pp. 338, 341). Therefore, hypoproteinemia might be a logical expectation in CF patients. Infants with CF have, in several reported instances, exhibited a combination of hypoproteinemia, edema, and anemia; however, the frequency of these cases is not especially high (e.g., 5 percent in one clinic population) and has been attributed to an inability to metabolize soy protein formula (Fleisher et al., 1964; Lloyd-Still, 1983a). Studies of older individuals, in the early and middle childhood years, have suggested some protein-specific metabolic

inadequacies accompanied, however, by adequate amino acid absorption for the digested proteins (Chase, Long & Lavin, 1979). Additional research (Vaughan et al., 1978) has identified a particular protein, low-density lipoprotein, which is involved in the transport of vitamins E and K, carotene, cholesterol, and linoleic acid, as present in reduced levels in CF patients. Such findings are consistent with current observations of possible protein-specific and amino acid-specific deficiencies associated with CF (Lloyd-Still, 1983a); deficits which could be important for fatty acid metabolism and transport. However, generalized, major protein deficiencies have not been reported for CF with the exceptions of treatable fecal nitrogen loss in CF infants and the hypoalbuminemia reported for older individuals experiencing cor pulmonale (Chase, Long & Lavin, 1979; Lloyd-Still, 1983a).

A second, and perhaps more significant, exocrine pancreas deficiency is the inadequacy or absence of pancreatic lipase secretions. Pancreatic lipases are responsible for the hydrolysis of long-chain fatty acids from dietary triglycerides (Chase, Long & Lavin, 1979, p. 338). It is this deficit in pancreatic lipases which results in the gross steatorrhea associated with CF (Lloyd-Still, 1983a). This deficiency has also been credited with the reduction of the essential fatty acid, linoleic acid, in over 50 percent of CF subjects in one

study (Chase & Dupont, 1978). Linoleic acid is important to the control of prostaglandin synthesis (Robinson, 1972). A specific prostaglandin, $F_{2\alpha}$, which is associated with bronchoconstriction and pulmonary vasoconstriction, experiences increased biosynthesis in the absence of linoleic acid. This poorly controlled biosynthesis has been hypothesized to contribute, over time, to the progressive pulmonary disease characteristic in older CF patients (Chase, Long & Lavin, 1979, p. 339).

The relationship between fat malabsorption and lipid-soluble vitamin deficiencies is, for the most part, beyond hypothesis. The effects of deficits in vitamins A, D, and E are well documented (Goodhart & Shils, 1980; Robinson, 1972). Vitamin A is necessary for night vision, epithelial membrane maintenance, and optimal growth and development (Chase, Long & Lavin, 1979). In studies involving laboratory animals, hypovitaminosis A produced alterations in ciliated cells of the lung, bronchiectasis, and pancreatic duct metaplasia with pancreatic atrophy (Smith et al., 1972). Associations between vitamin A deficiency and pulmonary disease were demonstrated by Congdon et al. (1981).

Vitamin D is especially important for the regulation of calcium and phosphorous concentrations in humans (DeLuca, 1980). Consequently, a deficiency in this vitamin might be expected to be registered in bone and dental

development, as well as muscle metabolism (Chase, Long & Lavin, 1979; DeLuca, 1980). In extreme cases of hypovitaminosis D in otherwise normal individuals, rickets, widened metaphyses, cupping and fraying of long bones, and/or skeletal radiolucency have been observed. Such findings are very rare in individuals with CF (Chase, Long & Lavin, 1979). In one vitamin status study with CF patients (Congden et al., 1981), serum 25-hydroxycholecaciferol, the major circulating vitamin D metabolite, was not uniformly low; and when it was reduced, supplementation had no effect. Other studies do report reduced serum vitamin D metabolite levels with a concomitant bone density reduction (Hahn et al., 1979; Hubbard et al., 1979). However, no consistent hypovitaminosis D effects are known for CF.

Vitamin E (tocopherol) is recognized for its ability to protect nutrients like vitamin A and some fatty acids from oxidation (Chase, Long & Lavin, 1979; Horwitt, 1980). It also is important in controlling the rates of synthesis for three prostaglandins; E_1, E_2, and $F_{2\alpha}$ (Chase, Long & Lavin, 1979). Just as in linoleic acid deficiency, bronchoconstriction and pulmonary vasoconstriction problems can be aggravated in vitamin-E-deficient individuals. From work with laboratory animals it has been suggested that vitamin E malabsorption may exacerbate infections in CF patients (Tengerdy et al.,

1973). In the study by Congden et al. (1981), serum vitamin E concentrations were very low and associated with the severity of steatorrhea in 90 percent of the CF patients tested. Chase and Dupont (1978) found that CF patients receiving vitamin E supplementation still had elevated prostaglandin $F_{2\alpha}$ levels.

The evidence for the uptake and utilization of minerals, especially the trace metals, by individuals with CF is far from complete. Zinc, known to be valuable for normal growth in humans (Hambridge, 1977; Li & Vallee, 1980), facilitates vitamin A transport (also important for optimal growth), and acts as a coenzyme in over 40 reactions (Chase, Long & Lavin, 1979). Normal, marginal, and low zinc levels have been reported for CF patients, with consistent association with delayed growth and development (Chase, Long & Lavin, 1979; Lloyd-Still, 1983a).

Another metal, selenium, has been suggested to be reduced in the plasma of CF patients. Selenium can act as an antioxidant in the absence of vitamin E and lineolic acid (Chase, Long & Lavin, 1979). Therefore, deficiencies in selenium could possibly prove aggravating to pulmonary problems in CF. Conclusive evidence is not yet available (see Elliott, 1976).

Iron uptake and storage have been examined in growing patients with CF. When compared to controls, CF patients demonstrate normal iron absorption patterns

(Heinrich et al., 1977); that is, when iron stores are low, absorption increases and vice versa. CF patients experiencing acute infection may show drastic decreases in hemoglobin though, due to storage in the liver during such situations. The same may be true for zinc (Lloyd-Still, 1983a).

Individuals with CF seem capable of digesting many carbohydrates to obtain energy. Although pancreatic amylase activity is absent in the 85 percent with pancreatic insufficiency, an enhancement of salivary amylase activity in many CF patients facilitates, with the aid of intestinal maltase, starch digestion (Lloyd-Still, 1983a). Some patients do require enzyme supplementation to tolerate starch. Glucose absorption is normal in CF patients during most of their development as is that of the disaccharides (Lloyd-Still, 1983a). The absorption of the pentose xylose appears increased when compared to that for controls (Lloyd-Still, 1983a). Energy deficiencies in CF individuals would most likely be related to deficits in fat stores and some vitamins. Chase, Long, and Lavin (1979, p. 339) advocate dietary supplementation with medium-chain triglyceride to minimize this deficit. However, Rosenlund et al. (1977) report no improvement, as evidenced by growth data, following such supplementation.

Respiratory System Involvement

With the exception of those neonatal fatalities attributable to meconium ileus, CF morbidity and mortality are predominantly related to the progressive pulmonary involvement characteristic of the syndrome (Lloyd-Still, 1983b; Wood, Boat & Doershuk, 1976). The lungs of most autopsied CF neonates and infants (under six months of age) appear normal with occasional, and very rare, observations of increased mucous secretion and initial obstruction being reported (DiSant'Agnese & Farrell, 1976). However, the nearly inevitable pulmonary complications do set in rather insidiously, presaged by hyperplasia, hypertrophy, and obstruction of the submucosal glands of the trachea and major bronchi (Lloyd-Still, 1983b; Wood, Boat & Doershuk, 1976). Escalation of bronchial involvement subsequently occurs, evidenced by goblet cell metaplasia of the bronchiolar epithelium and mucous plugging of the peripheral air passages (Wood, Boat & Doershuk, 1976, p. 843). A demonstrated increase in the basal rate of mucus-secreting epithelial cells complicates the situation greatly; but, no basic abnormality has been elucidated to explain this (Sturgess, 1981).

Respiratory infections are the usual consequences of these pathological modifications with bronchitis and bronchiolitis prominent. Antibiotic therapies are, of course, applied in these instances, but the basic problems

of the respiratory tract are not alleviated and "a vicious cycle of obstruction, chronic infection, and more tissue damage develops" (Wood, Boat & Doershuk, 1976, p. 843). Atelectasis, bronchiectasis, bronchiolectasis, peribronchial fibrosis, and airway obstruction all contribute to the progressive deficits in pulmonary function and consequent death in more than 95 percent of the CF patients who did not succumb to meconium ileus (Wood, Boat & Doershuk, 1976, pp. 843-844; Lloyd-Still, 1983b, p. 167).

As respiratory involvement progresses in CF the initial lesions in the peripheral airways, which often are indicated by increased alveolar-arterial oxygen differences resulting from abnormal distribution of ventilation, are succeeded by large airway obstructions (Wood, Boat & Doershuk, 1976, p. 844). Such progress impacts directly on pulmonary function in individuals with CF. Maximum mid-expiratory flow and forced expiratory volume is decreased, residual volume is increased (a result of lost elastic recoil and air trapping), and vital capacity is decreased (Lloyd-Still, 1983b; Russell et al., 1982; Wood, Boat & Doershuk, 1976). These pathological changes, although quite variable and often responsive to therapies, may be associated with increases in respiratory rate and decreased exercise and work tolerance, as many patients with CF are inefficient ventilators compared with others without CF (Cerny, Pullano & Cropp, 1982).

Symptoms typical to individuals with pulmonary complications of CF include cough, digital clubbing, costal flaring, and increased anteroposterior chest diameter from the increased work of breathing (Wood, Boat & Doershuk, 1976). Some individuals with CF are essentially asymptomatic for a substantial time during their lives; such manifestations may be related to early diagnosis and effective therapies or to phenotypic heterogeneity in syndrome composition or severity (Barbero, 1982; Scully et al., 1977; Sing et al., 1982). However, susceptibility to viral and/or bacterial infection is probably enhanced in CF subjects and exacerbation leading to pneumonia, bronchitis, and bronchiectasis is not uncommon for previously mildly afflicted individuals (Wood, Boat & Doershuk, 1976; Lloyd-Still, 1983b). With the development of bronchiectasis, pulmonary involvement tends to intensify rapidly giving rise to more frequent complications, irreversible pathological progression, cor pulmonale, respiratory failure, and death (Lloyd-Still, 1983b, p. 167).

Cystic Fibrosis and Development

Retarded growth and development were associated with CF even before it was recognized as a distinct clinical entity and referred to as "congenital pancreatic infantilism" (Clarke & Hadfield, 1924). Traditionally, pancreatic insufficiency and its resultant malnutrition have

been credited with observed delays by many of the clinicians dealing with this disorder (e.g., Barbero, 1976; Chase, Long & Lavin, 1979; Kraemer et al., 1978; Lloyd-Still, 1983a). Other researchers, however, have suggested strong associations between growth parameters and the severity of pulmonary involvement instead (e.g., Kreissl et al., 1972; Sproul & Huang, 1964). Yet another, perhaps more realistic perspective, recognizes the likelihood that delayed growth and development observed for CF is attributable to the combined influences of gastrointestinal and pulmonary involvement and possibly to their effects on endocrine functions as well (Green, 1983; Wood, Boat & Doershuk, 1976).

Clinical observations of compromised growth and development in CF have included poor weight gain, slow statural increases, and retarded skeletal maturation in both females and males. Delays in female sexual maturation, as evidenced by age at menarche, as well as dysmenorrhea and amenorrhea have been reported. Male sexual development has been indicated to be somewhat delayed in individuals with CF; yet, with the exception of aspermia, due to epididymal, vasa deferentia, or seminal vesicle anomalies, their sexual maturation is normal (Holsclaw et al., 1971; Moshang & Holsclaw, 1980; Green, 1983; Wood, Boat & Doershuk, 1976). However, in research reported by Corey (1980), the number of CF patients studied at the

Toronto clinic who experienced any measurable delays in growth and development was very small; proving an exception to the "rule."

Considering the nature of the exocrine pancreas dysfunctions and the concomitant possibilities for maldigestion and malabsorption of proteins, lipids, lipid-soluble vitamins, and minerals, it is not surprising that so much attention has been given the relationships between nutrition and development in CF. Yet, contrary to earlier claims of recommended daily allowances (RDA) of up to 150 percent of the normal being necessary for CF patients, recent work indicates RDAs between 52 and 93 percent (Lloyd-Still, 1983a, p. 228). The evidence suggests that growth in CF is a function of inadequate calorie consumption and that appropriate supplementation reverses the caloric imbalance and restores normal growth (Hubbard, 1980; Lloyd-Still, 1983a; Chase, Long & Lavin, 1979). Restoration in these instances is apparently evidenced as catch-up growth in weight moreso than in other parameters (see, e.g., Barclay & Shannon, 1975; Ellis & Hill, 1975; Kraemer et al., 1978).

The interrelationship between CF nutritional complications and severity of pulmonary symptoms seems well established in the literature (Chase, Long & Lavin, 1979; Lloyd-Still, 1983a; Shepherd, Cooksley & Cooke, 1980); and, the relationship between pulmonary disease stress

and CF growth delays has been equally well documented by a few auxological investigations. In one of the first attempts at providing information on the growth patterns of individuals with CF, Sproul and Huang (1964) conducted a mixed longitudinal study of growth in stature and weight, as well as skeletal development, for 50 subjects. They described significant retardation in the growth parameters for all age groups, especially the preadolescent and adolescent classes, and a delay of skeletal development in 38 percent of the subjects. Growth retardation, indicated by height and weight measures, was significantly correlated with the severity of the pulmonary disease, but not with the degree of pancreatic insufficiency. Following therapeutic intervention, antibiotics for pulmonary infections and enzyme supplementation for pancreatic insufficiency, Sproul and Huang reported catch-up weight gains, but no concomitant linear velocity or skeletal maturation rate increases [(1964, p. 674) n.b., the latter was not examined after intervention]. In explanation of the growth delay--pulmonary severity association, Sproul and Huang hypothesized (1) acidosis, (2) poor arterial oxygen saturation, and/or (3) increased oxygen work of breathing as causal (1964, p. 674).

In a more recent study by Kreissl et al. (1972), the physical growth and development of 53 subjects with

CF was evaluated for weight, weight velocity, height, height velocity, and skeletal age. Like that of Sproul and Huang (1964), this study elicited a high correlation between the two weight parameters and disease severity. No such relationship was obtained for the statural or skeletal age variables. However, Kreissl et al. (1972, p. 108) reported mild to moderate skeletal retardation in approximately 88 percent of their subjects, opposed to the 38 percent of Sproul and Huang (1964). Acknowledging difficulties of making direct comparisons between their results and those of Sproul and Huang due to the use of different standards and evaluation systems, Kreissl et al. (1972, p. 108) also offer (1) better, more intensive therapeutic practices in the nine years since the Sproul and Huang study, and (2) the possibility of the 1972 sample being biased by the fact that patients with more progressive forms of CF had died prior to receiving medical care. They do conclude, however, that in their sample, inadequate energy for growth is responsible for retardation among the parameters evaluated and that during childhood this energy deficit is related to inadequate caloric uptake while in adolescence, hypoxemia due to pulmonary damage becomes a possible contributor (Kreissl et al., 1972, p. 108).

Endocrinological studies of growth and development in CF have so far failed to discern whether retarded

growth and developmental delays are secondary to malnutrition or pulmonary dysfunction (Green, 1983). Green, Fefferman, and Nair (1967) discovered that CF patients experienced elevated fasting somatotropin levels with poor responses to induced hypoglycemia similar to, but of lesser magnitude than, conditions present in kwashiorkor, a disorder of acute protein deficiency with adequate calories (Frisancho, 1981, p. 178). Later reports (Biswas et al., 1976; Handwerger et al., 1969) contradicted these earlier findings, while a report by Milunski et al. (1971) has supported the finding of anomalous somatotropin responses indicative of malnutrition. As somatotropin appears to be present in normal or elevated levels in CF patients, speculation arose concerning the possibility of decreased somatomedin activity in these individuals. Again, different studies yielded contradictory conclusions (Green, 1983).

As a secondary complication to the administration of iodides to CF patients, hypothyroidism and goiter have been observed (Green, 1983). Such a response is contrary to that seen in normal individuals and exceeds that reported for asthmatic individuals (Falliers et al., 1966). Several studies have failed to elucidate an intrathyroidal defect in CF to account for the abnormal response to iodides (e.g., DeLuca et al., 1982). Thyroxine (T4) levels are reportedly normal in CF patients, as are those

for the thyrotropin (thyroid stimulating hormone); however, serum tri-iodothyronine (T3) is decreased in much the same pattern as that found in protein-calorie malnutrition patients (Burmudrez, Surks & Oppenheimer, 1975). CF patients may be classified as subclinically hypothyroid (DeLuca et al., 1982); but the mechanism for this abnormality, as well as its implications, if any, for growth and developmental delay in CF are as yet unknown (Green, 1983).

Therapeutic administration of anabolic steroids in one study produced increases in height and weight, as well as advances in skeletal age and male genital maturation in CF subjects (Dennis & Panos, 1965). Unlike unafflicted subjects' responses to such intervention, individuals with CF showed greater increases in linear metrics than in weight; suggesting that malabsorption of nutrients primarily affects weight gain in CF and that retardation in other parameters is influenced by different factors, perhaps endocrine. According to Green, "the primary problem with the [endocrine] studies has been a failure to correlate . . . results with specific scoring systems of either pulmonary dysfunction or states of malnutrition in the study population" (1983, p. 334).

Rationale for Study

The inability to conclusively demonstrate a causal relationship between either pulmonary disease severity or pancreatic insufficiency and selected growth parameters in CF is not only characteristic of the endocrinological studies. In the few auxologic investigations conducted to date no consistent associations have been obtained. In fact, as indicated in the preceding section, the results of the more influential studies are somewhat contradictory (Kreissl et al., 1972; Sproul & Huang, 1964). The failure on the part of these studies to consistently identify the pathophysiological condition most responsible for growth retardation and developmental delay in CF may be explained by any of the following alternatives.

As Kreissl et al. (1972) observed, inconsistencies in the results of different studies may be attributable to their utilization of different evaluation methods and standards. For example, Sproul and Huang (1964) employed the Greulich and Pyle radiographic atlas (1959) for the evaluation of skeletal development and the longitudinal "Boston" percentiles (Stuart, 1959) for growth metrics, while Kreissl et al. (1972) used the TW1 method (Tanner, Whitehouse & Healy, 1962) for skeletal maturational assessments and the Tanner, Whitehouse, and Takaishi (1965) standards for growth distances and velocities.

Differences in methodology might very well affect inter-study comparability.

Sampling error may be another contributor to the observed discrepancies. In the studies reviewed above, subjects were usually obtained from a single CF clinic and, consequently, were often quite small: for Dennis and Panos (1965) n = 31, for Kreissl et al (1972) n = 53, for Moshang and Holsclaw (1980) n = 80, and for Sproul and Huang (1964) n = 50. When compared to the available patient populations, these samples are probably quite representative; or, at least, the best obtainable under the specific clinical circumstances. However, it is possible that given different mortality rates, as speculatively advanced by Kreissl et al. (1972), or considerable phenotypic heterogeneity, as indicated by Corey (1980), Gaskin et al. (1980), and Sing et al. (1982), that samples, biased as to disease severity and/or syndrome composition, were examined in the different studies.

There is yet another alternative; the exploration of which might prove profitable for understanding the patterns of growth and development associated with CF. This alternative requires a modification of perspective from that of proximate auxology to that of ultimate auxology. Such a shift places CF developmental variation within a phylogenetic framework and brings to the fore a possibility which is examined in this dissertation research.

It is suggested herein that, in addition to the employment of different methods and standards, and the likelihood of differentially biased samples, the explanation for delayed growth and development in CF may not be directly related to the severity of either pancreatic insufficiency or pulmonary involvement. Consequently, efforts to elucidate which of these manifestations best predicts retarded growth and development in CF have been relatively unsuccessful. It is further suggested that rather than being a pathological response to disease stress during development, the pattern of growth and development associated with this disorder is an example of functional adaptation to CF.

As a functional adaptation the delayed growth and development observed in many individuals with CF may be either a genetic adaptation or an acclimatizational response to the disease stress. If genetic adaptation, then CF development would represent a norm of reaction, specific to those inheriting the disorder, providing some relative advantage in terms of maintenance of function, survival, and/or reproduction. This inherited norm of reaction would be somewhat canalized, or developmentally buffered, such that within the normal range of limitations imposed by the environmental stressors which selected it in past generations, individuals inheriting it would display a recognizable variant of phenotypic development.

In the case of CF that recognizable ontogenetic variant would include delayed development.

Delayed sexual and skeletal maturation, associated with relative deficits in height and weight when compared to standards, has been reported for juveniles experiencing hypoxic stress at high altitudes in South America (Frisancho, 1978, 1976, 1969; Haas, 1976; Mueller et al., 1980, 1978). These alterations in developmental rates have been inferred to be functionally advantageous in response to high altitude hypoxia insofar as they decrease the energy required for growth and development by slowing growth velocities and extending the postnatal growth period (Frisancho, 1981; Moore & Regensteiner, 1983). The results of these ontogenetic modifications are reproductively capable adults who, although slightly smaller than standards, display no compromised function related to their slower progress. Similar observations have been made for CF patients, who, although apparently retarded in metric growth, skeletal, and sexual maturation, ultimately approach normal adult statural ranges (Green, 1983). As genetic explanations have been advanced for the corresponding patterns in high altitude situations (Beall et al., 1977; Palomino, Mueller & Schull, 1979), this seems a reasonable hypothesis to examine in CF.

However, developmental homeostasis may also be maintained in the face of environmental adversity by

acclimatizational means. In studies of developmental delays at high altitudes an equal, if not greater, number of researchers have recognized acclimatization as the process responsible for more differences than genetic adaptation (Moore & Regensteiner, 1983). Metric changes, especially in weight, body composition, and circumferences have been determined to be related to the changing exigencies of life at various altitudes and, consequently, various intensities of hypoxic stress. Additionally, as with lowland dwellers, it has been reported that some of the growth-related responses to hypoxic stress are dependent upon the time of exposure to the stress; that is, individuals exposed to the stress for a longer portion of their development experience greater alterations (Frisancho, 1981). This is analogous to the experiences of clinicians and researchers who suggest an inverse relationship between age at diagnosis and degree of growth delay in CF (Lubin & Bonner, 1978; Orenstein et al., 1977). Consequently, the hypothesis that a CF developmental pattern is an acclimatizational response which slows development, thus redistributing growth-related energies with minimal functional compromise, as evidenced by the attainment of nearly normal adult statures in those who survive, is also worthy of examination.

Hypotheses

The study reported in this dissertation tests the general hypothesis that the pattern of delayed development often observed in CF is a functionally adaptive, rather than pathological, response to the stresses imposed by the chronic hereditary disorder itself. In order to discriminate among the alternatives of genetic adaptation, acclimatization, and pathology the following specific hypotheses were advanced concerning the patterns of relationship among dental, skeletal, and sexual maturation in growing individuals with CF.

1. If dental maturation is normal, but skeletal and sexual maturation are retarded and show a significant correlation with a clinical score of disease severity, then CF development is a pathological response to disease stress. Both skeletal and sexual maturation have been demonstrated to be very sensitive to the stresses of malnutrition, hypoxemia, infection, and endocrine dysfunction which all are known to present to some degree in CF. Dental maturation, as indicated by degree of crown and root formation, has not shown such environmental sensitivity. Consequently, if CF development is symptomatic of the severity of the disease, delayed maturational responses in sexual and skeletal development, similar to those observed for other systemic disorders (reviewed earlier in this chapter) would be expected. Additionally,

the magnitude of these delays would be expected to be dependent upon the severity of disease involvement.

2. If dental maturation is normal, skeletal and sexual maturation are retarded, the correlation between the latter and a clinical score of disease severity is insignificant, but the correlation with age at diagnosis is significant, then CF development is an acclimatizational response to disease stress. As in hypothesis 1, the differential response of the dental system when compared to that for sexual and skeletal systems is explicable in terms of the previously discussed stability of the former. The lack of significant response from the less stable, more sensitive, developmental indicators to disease severity accompanied by a significant association with age at diagnosis would be an intimation of developmental acclimatization. To distinguish these as results of developmental acclimatization as opposed to prior developmental insult, two avenues of inquiry were established. First, in the case of developmental acclimatization, no evidence of a catch-up phenomenon would be expected. Second, no indication of compromised function resulting from the developmental pattern should be elucidated.

3. If dental, skeletal, and sexual maturation are similarly retarded and exhibit an insignificant correlation with a clinically derived score of disease severity

then CF development is a Functional adaptation, a primarily genetic response to disease stress. In this hypothesis, retardation of dental development is the key feature. Demonstrably stable in the face of environmental pressures, including systemic disease stress, dental development would not be expected to undergo significant retardation unless some change in its maturational program had been affected. In addition, a significant correlation among dental age retardation and that for sexual and skeletal systems is not observed in standard populations and would be indicative of some overall modification of the organism's developmental instructions. Lack of significant correlation with disease severity would eliminate a unique syndrome-development interaction as an explanation.

Some Considerations

At this juncture it might be worthwhile to briefly review some points implicit in these hypotheses. First, the testing of the general proposition concerning the functionally adaptive value of a pattern of development associated with CF requires, as noted previously, a change in perspective. In this hypothetical context a developmental pattern, normally viewed as clinical evidence for pathology, must now be considered as a phenotypic character. Additionally, an inherited chronic disorder, usually

perceived as part of the individual's phenotype, must be recast as an environmental, albeit internal, variable exerting its influence on phenotypic characters. This is not a particularly demanding requirement, but, as in the case of the necker cube illusion (see Dawkins, 1982, p. 1), a constant focus is elusive.

Second, the term "growth" does not appear in the hypotheses. Its absence is more than a quirk of style. Although the vast majority of auxological observations in CF are concerned primarily with metric growth parameters, these might be the least instructional in a study such as this which is interested, not in the fact that clinicians perceive height and weight deficits, but in how these deficits occur. Growth is the result of developmental regulations, whether by ontogenetic accident or exquisite genetic program (see, e.g., Lewin, 1984). Consequently, the focus on development that is employed in this study proves more appropriate in the consideration of questions of functionally adaptive ontogenetic responses to disease. In addition, this study, while dealing with a traditional problem in CF auxology, collects maturational data not previously reported in the literature.

Third, it should be noted that there exist thirty-two possible combinations of the five variables included in the hypotheses. Hence, there exist thirty-two

possible hypotheses. The twenty-nine other possibilities were not explored as (1) they were not considered possible following a review of the literature on maturational indicators and (2) were not indicative of any of the three causes for delayed development being considered in this study.

Prior to presenting the research, a fourth consideration is offered. If the general hypothesis is not refuted, the use of standards of growth, derived from the longitudinal survey of individuals without CF, to evaluate the clinical course or efficacy of therapy for CF patients may bear reappraisal. The elucidation of a nonstandard, non-pathological, typical pattern of development for CF subjects would indicate the need for consideration of a more extensive survey of CF developmental parameters and the possible establishment of syndrome-specific standards.

Summary

This chapter should be considered the theoretical and informational foundation for the research which will be reported in subsequent chapters of the dissertation. Initially, the substantive purpose of the study was briefly identified: to examine the pattern of development in selected maturational parameters for individuals with the chronic hereditary disorder, cystic fibrosis; to determine whether a variant pattern of development,

corresponding to previous observations for growth variables, is present in these individuals; and to determine if that pattern is indicative of pathology or functional adaptation. As a means of placing the research in its proper perspective, the history of auxological investigation and its relationship with and contributions to biological anthropology were discussed. Inasmuch as this study represents an attempt to apply the principles and concepts of evolutionary biology to a problem of clinical pediatrics, the relationships among relevant aspects of ontogeny, phylogeny, and functional adaptation were examined in some detail. The concepts of growth and development were contrasted and a review of the major features of skeletal, dental, and sexual development was presented in order to demonstrate the bases for comparisons to be reported in later chapters. A discussion of cystic fibrosis followed, emphasizing pertinent pathophysiological aspects so that the potential for pathological effects on growing individuals afflicted by this disorder could be appreciated. A brief review of growth-related cystic fibrosis research was presented to explore areas where this study might make worthwhile contributions and to indicate the rationale for the approaches to be employed in this investigation. Finally, the specific hypotheses

to be tested in this study were elaborated, their support consisting of the bulk of observations reported previously in this chapter.

CHAPTER II

MATERIALS AND METHODS

Conduct of Research

This study was conducted at the Children's Hospital and at The Ohio State University in Columbus, Ohio, U.S.A. Preliminary contacts with paramedical, administrative, and technical personnel at the Children's Hospital were made between June and September 1982 during the drafting of the research proposal. In collaboration with Dr. K. S. McCoy of the Pulmonary Division in the Department of Pediatrics at the Children's Hospital, the proposal was refined and the clinical protocol was drafted in October and November 1982. At that time initial application for research funding was made to several sources. In January 1983 the proposal and protocol were submitted to the Human Subjects Review Committee at the Columbus Children's Hospital. Committee approval was granted in May 1983.

Personal interviews, to explain the proposed study and to recruit subjects, were conducted with the CF patients and their parents following regularly scheduled appointments with their physician, Dr. G. A. Young.

These interviews were initiated in May 1983 and were conducted in offices adjacent to Dr. Young's examining rooms in the Children's Hospital Professional Building throughout the study. Initial clinical data collection began in October 1983 and continued until April 1984. All data collection occurred at the Columbus Children's Hospital's facilities.

Data management and analysis were completed in the Department of Anthropology at The Ohio State University employing the computer facilities of the Instructional and Research Computer Center. This phase of the study began in late May and was completed in June 1984.

The Research Site

The Columbus Children's Hospital was selected as the research site for several reasons, not the least of which were its geographic and academic proximities to The Ohio State University. As a recognized Regional Cystic Fibrosis Center, Children's Hospital possessed the requisite diagnostic and therapeutic facilities necessary to support a sizeable patient population (approximately 220 individuals). Although there are CF clinics in other Ohio cities, the Columbus clinic treats patients from nearly every region of the state and from the neighboring states of Indiana, Kentucky, and West Virginia.

The familiarity of this facility with CF patient care and research was perceived as a potential benefit to the study. One physician, Dr. Young, has been solely responsible for the medical care of the vast majority of the clinic's patients for approximately twenty years. His office maintains extensive records and is knowledgeable concerning nearly every aspect of the patients' lives. The experience of both the clinic and the patients with past and other current projects augered well for the conduct of this research. Past studies, primarily in nutritional biochemistry and psychosocial aspects of CF, were directed by Dr. A. H. Lubin. Currently, Dr. McCoy is directing CF-related research in pulmonary and neurophysiology with both human and nonhuman models. Consequently, the Columbus Children's Hospital and CF clinic environment were perceived as being favorable to the successful conduct of this auxological study.

Subjects

Developmental data necessary to test the advanced hypotheses were obtained from individuals currently involved in clinical care and suveillance at the Regional Cystic Fibrosis Center at the Columbus Children's Hospital. The sample consisted of 50 individuals, 23 females and 27 males, between the ages of $7\frac{1}{2}$ and $17\frac{1}{2}$ years. This sample represented approximately 53 percent of the 95

individuals within the specified age range in the clinical population of approximately 220. The original protocol had called for 60 subjects, 30 females and 30 males, with 3 members of each sex in each of 10 one-year age classes. However, three cases of rejection, a few instances of chronic appointment canceling, and an occasional equipment malfunction precluded the attainment of those goals. Nonetheless, this sample size was consistent with those of previous CF growth and development studies (e.g., Kreissl et al., 1972; Sproul & Huang, 1964); the age range of the subjects corresponded to the periods during which developmental changes could be evaluated by the selected maturational indices (Demirjian, 1978; Tanner, 1962; Tanner et al., 1975); and the composition of the age classes was amenable to cross-sectional analysis (Tanner, 1978b, 1978c). Table 1 presents the age class composition for the sample.

The patients who volunteered to be subjects of this study were deemed to be fairly representative of the clinical population by the attending physician (a retrospective appraisal). However, no criteria except a positive diagnosis of CF, being under the clinical care of Dr. Young, and being within the age range of the study, were employed in determining whom to recruit. The sample includes patients from nearly all the geographic regions represented in the survey of the general patient

TABLE 1

CF STUDY SAMPLE COMPOSITION BY AGE-CLASS AND SEX

Age Class	Age Range (Years)	Number of Females per Class (% Total)	Number of Males per Class (% Total)
8	7.50- 8.49	3 (13.0)	3 (11.1)
9	8.50- 9.49	3 (13.0)	3 (11.1)
10	9.50-10.49	1 (4.3)	2 (7.4)
11	10.50-11.49	2 (8.7)	3 (11.1)
12	11.50-12.49	3 (13.0)	3 (11.1)
13	12.50-13.49	3 (13.0)	3 (11.1)
14	13.50-14.49	2 (8.7)	2 (7.4)
15	14.50-15.49	2 (8.7)	3 (11.1)
16	15.50-16.49	1 (4.3)	3 (11.1)
17	16.50-17.49	3 (13.0)	2 (7.4)
	Totals	23 (99.7)	27 (99.9)

population: 28 percent from the metropolitan Columbus area, 64 percent from other parts of Ohio, and 8 percent from outside the state. Additionally, a wide socioeconomic range was represented (G. A. Young, personal communication). The sample included only one individual, a 12-year-old female of subsaharan African heritage, who was not of Caucasian western European descent. Also included in the sample were a pair of siblings, a 15-year-old male and an 11-year-old female, plus one set of male second cousins of different ages. Beyond this information, no other known interrelationships among the subjects of this study obtain.

Research Variables

At its most basic level the objective of this study was to make an inference about the relationships among phenomena within a population based on the data contained in the sample. Dental, sexual, and skeletal maturation, disease severity, and two measures of chronological age were the phenomena. Growing and developing humans with CF comprised the population. The 50 individuals recruited from the Columbus Children's Hospital CF clinic made up the sample. A necessary prelude to making inferences about the behavior of these phenomena within the population was the measurement and description of them in the sample. The following approaches to that task were employed in this research.

Chronologic and Diagnostic Ages

In order to accurately assess the patterns of deviation from normative developmental standards in this sample, several different age determinations were obtained. All ages used in this study were decimal ages (Weiner & Lourie, 1982). Each subject's decimal chronological age on the date of data collection was calculated by subtracting the subject's decimal birth date from the decimal examination date according to the International Biological Programme's protocols presented in Weiner and Lourie (1982, pp. 14-15). The decimal chronological age,

age at CF diagnosis, and a variable referred to in this study as "CFage" were all obtained in a similar manner. CFage refers to the time since the diagnosis of CF in a subject, arrived at by subtracting the decimal date of diagnosis from that of the data collection. All dates were obtained from the attending physician's records and checked against the hospital's charts. An additional confirmation of the accuracy of these dates was acquired by requesting them from the subjects prior to the developmental data collection.

Growth Metrics

Although information on stature and weight was not required to test the hypotheses put forward in this research, preliminary observations on clinically derived growth metrics were made in order to corroborate the existence of deficits in the population from which the sample was drawn. Pulmonary function test charts and the attending physician's patient charts provided stature and weight measures for a majority of the 95 patients in the age range from which the sample was eventually obtained. Acknowledging the amount of observer error present in most clinical anthropometrics, a crude cross-sectional study was performed using National Center for Health Statistics height and weight percentiles (Hamill et al., 1949). The purpose of this brief inquiry was to avoid being in the

position of trying to elucidate developmental mechanisms for nonexistent growth delays.

Dental Maturity

The assessment of dental maturation in the subjects was accomplished by evaluating panoramic dental radiographs for recognized stages of crown and root calcification. A number of different approaches have been advanced for the assessment of dental maturity from radiographs (e.g., Demirjian et al., 1973; Fanning, 1961; Garn et al., 1958; Glesier & Hunt, 1955; Moorrees et al., 1963; Nanda & Chawla, 1966; Nolla, 1960). These approaches divide the development of the dentition into arbitrarily selected stages (Demirjian, 1979). Although some methods may require more effort to master, and questions concerning reliability have been raised about others, several additional criteria led to the choice of the system of Demirjian et al. (1973) for this study.

(1) This assessment system utilized a single panoramic radiograph of the entire mandibular dentition, rather than the multiple oblique jaw or single tooth exposures required by the other systems. Consequently, it was less inconvenient for the subject. (2) Its method of assessment of size changes in crown and root development was based upon relative dimensions and proportions, easily discerned by the researcher, instead of the

absolute values of the other systems. (3) Standards of dental development have been established for this system, based upon samples of 2,349 females and 2,047 males of French-Canadian origin (Demirjian, 1978). As the subject population was predominantly of western European descent, this system appeared all the more appropriate.
(4) Studies of intra- and inter-observer error have been completed for this system, and it was subsequently modified and refined. This has not been reported for the other systems (Demirjian, 1979).

Using this system of assessment, the panoramic dental films were examined for each subject. The seven left mandibular permanent teeth (excluding the third molar because of its highly variable expression) were assigned developmental ratings, corresponding to weighted maturity scores, in the following order: second molar, first molar, posterior premolar, anterior premolar, canine, lateral incisor, and central incisor. The rating was arrived at for each tooth by carefully comparing the tooth to the textual criteria, a sample radiograph, and a diagram for each of that tooth's eight developmental stages (as presented in Demirjian et al., 1973; Demirjian, 1978). For each stage there were either one, two, or three written criteria. If three developmental criteria were given, it was necessary that the first two be met for that rating to be assigned. If two criteria were

given, the presence of the first criterion was sufficient and necessary to assign the rating.

All X-rays were evaluated, on two different occasions, on a fluorescent photographic light board. The ratings were assigned, as advised (Demirjian, 1978, p. 428), with the unaided eye. Comparisons of relative lengths were made with a standard metal metric rule. If one of the seven left mandibular teeth to be evaluated was missing, its antimere, if present, was substituted (nb. on the two occasions that a tooth was missing its antimere was present).

On the two occasions that the panoramic dental films were evaluated, the assigned ratings for each subject's seven left manidibular teeth were recorded. Only after ratings had been recorded for all the subjects, were the corresponding weighted maturity scores obtained for each tooth and summed. The summed dental maturity score for each subject was converted to an estimate of dental age using the conversion tables provided by Demirjian et al. (1973, pp. 224-225) and the standard age-score centile distribution presented in Demirjian (1978, pp. 430-431).

Skeletal Maturity

As was the case for dental maturation, there have been a number of methods developed to assess the maturity

of the osseous skeleton (Gruelich & Pyle, 1959; Hoerr et al., 1962; Pyle & Hoerr, 1969; Roche, Wainer & Thissen, 1975; Tanner et al., 1975). After reviewing the many methods available, it was decided that the system of Tanner et al. (1975), commonly referred to as the TW2 method, would be employed. The TW2 method was perceived to present many of the same advantages as the dental maturity system adopted for this study. This was actually not surprising as Demirjian et al. (1973) modeled their dental system on an earlier version of the TW2 skeletal method. The TW2 method of assessment was an alternative to the atlas methods (e.g., Greulich & Pyle, 1959) of evaluating skeletal development from radiographs of the ankle-foot, knee, and hand-wrist complexes. Although touted by their users, the atlas approaches have always been somewhat suspect due to the high degree of subjectivity involved in their utilization (Roche, 1978; Tanner et al., 1975). High marks for accuracy and replicability have been achieved by veteran practitioners with the atlas systems only after they have established the combination of osseous centers which works best for them (see, e.g., Peritz & Sproul, 1971; Roche, 1978; Sproul & Peritz, 1971). However, convincing evidence that the TW2 approach is more reliable than the comparable Greulich-Pyle atlas methods has been amassed by several researchers (Acheson et al., 1963; Johnston et al., 1973; Roche, 1978).

The advantageous characteristics of this system, vis-à-vis this study, may be summarized. (1) As with the dental rating system, the TW2 method required only a single radiograph of the hand-wrist region. Correct positioning for this exposure was easily achieved, the required X-radiation dosage (8-10 millirads) was minimal, and the hand-wrist site was quite distant from the more radiosensitive areas in the growing subjects (Tanner et al., 1975, p. 41). (2) With this system, assignment of the ratings was based upon definite objective developmental criteria and utilized only relative measures for size comparison. (3) Tanner et al. (1975) have established standards for this method based upon the examination of over 7,700 radiographs for 1,317 females and 1,385 males from an average socioeconomic level in the U.K. Again, as the population of interest in this research project was predominantly of western European descent, these standards were deemed acceptable. (4) The reproducibility of TW2 skeletal age assessments by a self-taught assessor has been investigated (Beunen & Cameron, 1980) and found to be as good as that of assessors trained by the originators of the method or other experienced raters. (5) Just as the left mandibular dentition has been shown to be representative of dental development in general, the hand-wrist complex has been demonstrated, with some qualification, to be representative of the

skeletal system (Tanner et al., 1975). Although some hand-wrist bones have failed to exhibit high intercorrelations, selected ones have been claimed to correlate well with tibial centers, for example, and, consequently, provide a representative series for comparison (Roche, 1978; Tanner et al., 1975).

One hand-wrist radiograph was taken for every subject according to the methods outlined in Tanner et al. (1975). As with the dental assessment, ratings were applied to each of the hand-wrist films at two different times. Twenty of the 28 bones of this complex were evaluated in the following order: distal radius; distal ulna; metacarpals 1, 3, and 5; proximal phalanges 1, 3, and 5; middle phalanges 3 and 5; distal phalanges 1, 3, and 5; capitate; hamate; triquetral; lunate; scaphoid (or navicular); trapezium (or greater multangular); and trapezoid (or lesser multangular). Alphabetic maturity ratings were assigned by comparing each bone in the radiograph to the textual criteria, diagrams, and sample radiographs for each developmental stage presented in Tanner et al. (1975). The written criteria were the final arbiters in all cases, however; the diagrams and sample films being used primarily for preliminary identification. For each of the 20 bones, nine developmental stages were listed on the average. Each stage was characterized by one, two, or three written criteria. As when assigning the dental

ratings, if three criteria were listed, the first two had to be met before assigning the ratings; if two were listed, the first one, and so on.

The hand-wrist films were evaluated on the same photographic light table as were the dental films. Alphabetic ratings and their corresponding maturity scores were assigned and recorded for each bone. The maturity scores were not summed until the procedure had been completed twice for the total sample. The scores were summed and converted to bone ages for each of the subjects using the 20 bone score conversion tables provided for females and males in Tanner et al. (1975). Skeletal ages for the same individual were compared for agreement. If a difference of greater than 0.5 years was observed between the two ages, the radiograph was evaluated twice again at a later time (this was necessitated in five instances). If such a difference was not observed, the arithmetic mean of the two skeletal ages was used in the subsequent analyses.

Sexual Maturity

Sexual maturity, as indicated by the developmental condition of a series of secondary sexual characters, was assessed in all subjects according to the criteria established in Tanner (1962) and outlined in slightly modified form in Weiner and Lourie (1981). As this was perhaps the only well-elaborated system of assessing sexual

maturity in the literature for which standards had been considered (to this author's knowledge), the choice was not difficult. Employment of the system has been associated with relatively high accuracy and replicability among self-taught assessors (Weiner & Louri, 1981, p. 55). Additionally, the system is amenable to either cross-sectional or longitudinal surveys (Tanner, 1962, 1978b; Weiner & Lourie, 1981).

As they could be evaluated by direct observation (i.e., visual inspection) rather than palpation or some obtrusive method, the following features were examined in order to specify the stage of pubertal development attained by each of the subjects: female breast development, male external genital development, and female and male pubic and axillary hair development. In addition, the attainment of menarche in females was recorded. With the exception of axillary hair development and attainment of menarche, the modified Tanner system (in Weiner & Lourie, 1981) has divided the maturation of these features into five recognizable stages with explicit textual criteria and photographs for comparison. These stages ranged from no development in the juvenile subjects to adult development in the mature subjects (a discussion of the development of these characteristics was presented in Chapter I). Axillary hair was rated, in contrast, as being absent, present, or present in adult quantity and

distribution; a three-stage scenario. Experience of menarche was rated by the status quo method; menarche was recorded as either having occurred or not.

The direct observation of sexual maturity indicators was made by the comparison of the subject's features with the criteria and photographs in the text (Weiner & Lourie, 1981). Although the criteria had been committed to memory, the text was always referred to during the evaluations to avoid any greater subjectivity than was already present in the system. For females, axillary hair, breast and pubic hair development were assessed with the subject supine on the examination table, or in the case of one hospitalized patient, on a hospital bed. Subsequently, breast development was evaluated with the subject sitting up on the examination table to ascertain that the original evaluation was not influenced by position. Sexual maturity was evaluated in all females regardless of chronological age. Maturity ratings were assigned at the time of the evaluation. Following the physical examination the subject was asked if she had experienced menarche. This answer was corroborated by the attending physician and the parent. Development of axillary hair, pubic hair, and external genitalia in males was also evaluated with the subject in a supine position on the examination table (exceptions included two young males who wanted to stand during the examination; their wishes

were granted and the data were collected). The sexual maturity data were recorded for all males and comparisons were made to centile standards presented in Tanner (1962, 1978b).

All physical examinations of secondary sex character development were conducted in the presence of a parent or legal guardian. If the subject did not wish that individual to be present, a physician of the same sex as the subject was requested to assist in the assessment. All subjects were examined in hospital gowns, the appropriate portion of which was retracted to examine a particular character.

Disease Severity

Several methods for evaluating the severity of disease involvement in individuals with CF have been devised (Brasfield et al., 1979; Cooperman et al., 1971; Lester et al., 1980; Schwachman & Kulczcki, 1958; Taussig et al., 1973). These systems yield "clinical scores" which are used variously to assess the previous or current status of a patient in order to monitor the effects of therapeutic interventions and/or to evaluate a patient's prognosis (Lloyd-Still, 1983b). For this study a modified version of the Taussig-NIH prognostic scoring system (Taussig et al., 1973) was used.

This approach was based predominantly on the pulmonary parameters of CF. It incorporated the results of pulmonary function tests (vital capacity and forced expiratory volume), clinical complications such as hemoptysis, pneumothorax, cor pulmonale, pulmonary surgery, and the evaluation of the patient's pulmonary radiographs (Taussig et al., 1973). Although the system has been criticized as being difficult to use with subjects under the age of seven (Lloyd-Still 1983b), the same critics have suggested that it might offer a more accurate picture of preadolescent and adolescent subjects' clinical condition than the widely used Schwachman-Kulczycki (1958) score.

The pulmonary aspects of the Taussig-NIH score account for 75 percent of its points. As the remaining 25 percent of the score is contributed by metric and (what this researcher evaluated as) extremely subjective life style questions, the system was altered for this study by eliminating that last 25 percent. This modification was justified by the common acknowledgment in the literature that the predominant cause of debilitation and death in CF is the progressive pulmonary disease and that gastrointestinal involvement is reflected in and exacerbates the pulmonary condition (see DiSant'Agnese and Farrell, 1976; Lapey et al., 1974; Lloyd-Still, 1983b; Shepherd, Cooksley & Cooke, 1980; Wood, Boat & Doershuk, 1976). Consequently, it was believed that the pulmonary

indicators of the Taussig-NIH score would be sufficient and better than other available systems for assessing disease severity in this study.

The disease severity scores for the subjects were assigned in collaboration with Dr. McCoy of Children's Hospital's Pediatric Pulmonary Division. Pulmonary function charts, hospitalization charts, attending physician charts, and radiology files for each patient were obtained and examined by the pulmonary physician. Scores were assigned according to written criteria (Taussig et al., 1973) and recorded at that time by the researcher.

Management and Analysis of Data

All data acquired for each subject were recorded on data sheets modeled in accordance with suggestions of the International Biological Programme found in Weiner and Lourie (1969, 1981). Initial data management and subsequent analyses were completed using the Amdahl computer facilities of the Instruction and Research Computer Center at The Ohio State University. Data were submitted for computer analysis in terminal batch format by means of the WYLBUR editor subunit.

Sources of Error

All analyses are subject to error. In descriptive and inferential statistics there exist methods for estimating the degree to which parameters such as sample size,

sample mean, and dispersion of values about the mean may affect the drawing of inferences from one's data. In the statistical analyses conducted on these developmental measures packaged programs and routines which identify the amount of statistical error due to the quality of the data were employed. In addition, the use of these algorithms obviated, for the most part, anxieties concerning computational miscues on the part of the researcher.

There are, of course, other paths by which error may have been introduced into this study. Attempts were made to foresee such eventualities and avoid them. By focusing on developmental indicators rather than measures of growth, one potentially great source of error was eliminated. Unlike anthropometrics where measurement accuracy is dependent upon the skill of the investigator, calibration of the instruments, humidity, and barometric pressure (see, e.g., Albrecht, 1983; Cameron, 1978), the maturational indicators are assessed by establishing the presence or absence of explicit diagnostic events. In all evaluations a conscious effort was always made to assess directly from the written criteria, thus avoiding the opportunity to assign ratings based on such observations as "it's almost a stage 4." Measures of error in the developmental standards have been calculated and published.

Although it was not possible when evaluating sexual maturity in the subjects, all dental and skeletal maturity assessments were made without knowing whose radiographs were being examined. A code number between 1 and 60 was randomly selected, without replacement, for each patient's data sheet. The identification tags of the radiographs were masked and the films were filed with the data records until all subjects had been examined. Then the radiographs were evaluated. This was done to avoid any temptation to reevaluate a particular film because of personal knowledge of a subject's condition or recognition of a trend in the data.

Information obtained for disease severity scores was another potential source of error as observations on various clinical parameters made by different professionals under unknown circumstances were interpreted by another medical professional. It is for such reasons that the last 25 percent of the Taussig-NIH clinical score was eliminated. This left the results of pulmonary function tests, conducted under specified conditions with highly calibrated equipment, a chest X-ray, which the clinician could evaluate herself, and clinical observations by the attending physician as the remaining sources of minimal, but unmeasured, error.

One last opportunity for error was in the entering of data into the computer for analysis. All data were

entered using the WYLBUR editing subunit from a terminal with full screen editor capability. Data from record sheets were checked against the monitor. As an additional check, the input data matrix was requested on all computer printouts following analysis.

Analytical Procedures

All statistical analyses were conducted using BMD (Dixon 1977) and/or BMDP (Dixon et al., 1981) statistical software packages. Included were analytical procedures to obtain sample summary statistics for all variables in both female and male sex classes, plus the application of linear models to both raw data and principal components of standardized raw variates. Many of the approaches employed contain implicit assumptions concerning the nature of the distributions of the data in the populations about which inferences are being made. At first glance, the observations made in this study might not appear to be accommodated within a continuous distribution as they are events, not continuous variables. However, if maturational indicators are considered in terms of the proportion of a standard population in which a particular event has occurred, or stage has been attained, by the members of a given age class, the curve produced by plotting these proportions against age would closely approximate the Gaussian (Healy, 1978, p. 180). As this was the case

and since the actual distributions against which the sample data were compared were known, such questions were obviated.

In order to apply linear models and methods of analysis derived from them appropriately one must first determine if such tendencies exist in the data. To accomplish this, bivariate scatter plots of the raw developmental and disease variables were produced using the "Plot" subroutine of BMDP4R (Dixon et al., 1981). By examining these scatterplots linear trends in the data were ascertained.

Although all the developmental rating systems were very similar to one another, the analysis still had to contend with the fact that most of the variables were measured on various scales and in different units. Chronological, CF (i.e., years since diagnosis), dental, skeletal, and diagnostic ages were all measured or expressed in decimal years on an interval scale. Dental maturity scores, however, were measured on a scale from 0 to 100 points; skeletal maturity, on a scale from 0 to 1,000 points; sexual maturity, on an ordinal scale from 0 to 4 points; and disease severity, on a similar scale from 0 to 75 points. In each case 0 represented the most immature or least expressive value and the upper limit given referred to the adult or, in the case of disease severity, the most pessimistic, value (see Demirjian, 1978; Tanner

et al., 1975; Tanner, 1962; Taussig et al., 1973). Prior to the multivariate analyses the variables were standardized to ameliorate the effects of scale differences.

As multiple regression had been selected as one of the statistical methods the possible effects of multicollinearity had to be considered (Chaterjee & Price, 1977). These effects include inflation of the explanatory power of the regression, inordinately large standard errors for the regression coefficients, and heightened sensitivity of the regression model to changes in the numbers of cases or variables (Baumgartner & Mueller, 1984). The use of principal components as data in these analyses helps to avoid such problems.

The primary analytical method employed to test hypotheses in this study was regression on principal components. Principal components analysis is perhaps the most common form of factor analysis (Kashigan, 1982, p. 245). Its greatest utility is in the reduction of a larger collection of redundant, correlated variables to a smaller number of composite index variables which are uncorrelated yet retain the essential information of the original data set (Baumgartner & Mueller, 1984, p. 112). These composite variables are linear transformations of the raw variables and reflect the principal dimensions of covariation in the original data matrix (Baumgartner & Mueller, 1984, p. 113; Rummel, 1975). In PCA there

are as many weighted linear combinations of the input variables, or principal components, as there are variables. The principal components model may be expressed as:

$$C_i = b_{i1}Z_1 + b_{i2}Z_2 + \cdots + b_{ij}Z_j$$

where Z_j are standardized original variables, b_{ij} are the standardized regression weights which serve to maximize the variance explained by the patterns of intercorrelations among the original variables, and C_i are the new, uncorrelated components (after Baumgartner and Mueller, 1984, p. 113).

Principal components result, then, from the transformation and decomposition of the original data matrix employing either the correlation matrix(R) or the covariance matrix(S) for these original data with the matrix of linear transormations or eigenvectors(E) and the matrix of eigenvalues(λ) for the components (Baumgartner & Mueller, 1984; Mardia, Kent & Bibby, 1979). The eigen equation, expressing the relationships on which this process is based, is: (R or S)E = λE (Baumgartner & Mueller, 1984; Zegura, 1978). The first principal component is equivalent to the axis drawn through the multivariate distribution which accounts for the greatest proportion of the variance in that distribution (Baumgartner & Mueller, 1984; Kashigan, 1982; Mardia, Kent & Bibby, 1979). The

second and successive principal components account for ever decreasing portions of the remaining variance in the multivariate distribution (Kashigan, 1982).

In this study principal components analysis was exploited to obtain uncorrelated linear combinations of observations on developmental indicators which could be used as independent variables in regression analysis. Principal components analysis was conducted on the correlation matrix for the standardized variables; an ordered subroutine of the regression on principal components program, BMDP4R (Dixon et al., 1981). Following this decomposition to independent linear composites, the new variables were entered into multiple linear regression analysis in order to test the hypotheses concerning functionally adaptive development in CF.

Although any number of variables may be reduced to a few principal components for further analysis, some relevant criteria should always be established to discriminate the original variables to be decomposed. Additionally, criteria should be considered to identify the more salient dependent variables. In this study preliminary analyses of correlations among the original raw variables for the combined sex, female, and male samples accomplished this. A t-test of the correlations was used to identify correlation values of r showing significant departures from zero. The method used, described in

Edwards (1976, p. 84), employed the following identity:

$$t = \frac{r}{\sqrt{1-r^2}} (\sqrt{n-2})$$

where r is the correlation coefficient and n refers to the number of observations. Significant departures were recognized at the 0.01 level. The patterns of significant and nonsignificant associations were utilized as an aid for combining variables in subsequent analyses.

Summary

In this chapter, the basic materials and methods employed in data collection and analysis were reviewed briefly. The general time frame for key events in the conduct of the research on which this dissertation is based was presented. A description of the research site, Children's Hospital in Columbus, Ohio, was included to indicate its suitability as a location for the planned research into CF growth and development. The methods selected for the assessment of dental maturity, skeletal maturity, sexual maturity, and pulmonary disease severity in subjects with CF were introduced. Rationales for the selection of the systems of Demirjian et al. (1973), Tanner et al. (1975), Tanner (1962; modified in Weiner & Lourie (1981)), and Taussig et al. (1973) included (1) convenience to subjects, (2) accuracy and

replicability for self-taught assessors, (3) representativeness for the entire developmental or pathological system, and, (4) for the developmental indicators, the existence of established standards for comparison. A description of the general procedures followed in making the assessments on the variables was presented with special emphasis placed on adherence to the specifications for the various stages of maturation. The importance of this cannot be stressed enough for the maximization of replicability and objectivity in the analysis of developmental variables.

A review of potential sources of error for this study included error attributable to (1) sample parameters, (2) improper assessment techniques, (3) investigator bias, (4) utilization of multiple author records, and (5) data processing mistakes. Measures taken to minimize the probability of these sorts of errors were identified. The methods used in the analysis of the data with The Ohio State University's computer facilities were recounted briefly. The basic features of principal components analysis, a multivariate statistical method employed in the major analyses of this study, were described in order to make clear the reasons for its use. The software used to identify the patterns of relationships among the variables was indicated.

CHAPTER III

RESULTS AND OBSERVATIONS

Clinically Derived Growth Metrics

The preliminary examination of growth metrics recorded on pulmonary function test charts and in the patients' clinical records were suggestive of a clinical evaluation of growth delay. Employing diagnostic criteria adopted from Sproul and Huang (1964, p. 668), and presented in Table 2, the subjects of this rather unrefined survey exhibited clinically evident degrees of retardation in both stature and weight (see Table 3). Both females and males displayed these delays in the pattern often reported by physicians in which retardation in weight is more apparent than that for stature. However, in this brief survey females exhibited greater delays in both parameters than males; 70.8 percent showed retardation in height and 83.3 percent were retarded in weight compared to values of 53.8 and 65.4 percent of the males for the same characters.

A mean cross-sectional approach to these data supported the contention of metric delays also. Mean weights and heights for the ten age classes in this sample were

TABLE 2

CRITERIA FOR EVALUATING DEGREE OF RETARDATION IN HEIGHT AND WEIGHT IN SUBJECTS WITH CF (AFTER SPROUL & HUANG, 1964, p. 668)

Degree of Retardation	Height	Weight
None	Height Age (H.A.) ±9 mo. Chronological Age (C.A.)	Weight Age (W.A.) ±12 mo. C.A.
Mild	H.A. -12 to 18 mo. C.A.	W.A. -13 to 24 mo. C.A.
Moderate	H.A. -19 to 24 mo. C.A.	W.A. -25 to 30 mo. C.A.
Severe	H.A. -25 mo. C.A.	W.A. -31 mo. C.A.

TABLE 3

PERCENT OF FEMALES AND MALES WITH CF SHOWING DEGREES OF RETARDATION IN HEIGHT AND WEIGHT AS DERIVED FROM CLINICAL RECORDS

Degree of Retardation	Females		Males	
	Height	Weight	Height	Weight
None	29.2	16.7	46.2	34.6
Mild	33.3	29.2	19.2	26.9
Moderate	25.0	16.7	19.2	7.7
Severe	12.5	37.5	15.4	30.8
Mild-Severe	70.8	83.3	53.8	65.4

compared to National Center for Health Statistics standards (Hamill et al., 1979). All female means were below the 90th centile for stature and at or below the 50th centile for weight (see Table 4). One hundred percent of the males sampled were at or below the 50th centile for

both height and weight (Table 4). A plot of these mean metrics and their standard errors may be found in Figure 1 for females and Figure 2 for males. Preliminary observations did indicate growth-related delays in the patient pool from which the subjects were recruited.

TABLE 4

PERCENT OF MEAN CROSS-SECTIONAL HEIGHTS AND WEIGHTS AT OR BELOW STANDARD PERCENTILES IN FEMALES AND MALES WITH CF

	Females		Males	
Percentile	Heights	Weights	Heights	Weights
5th	10	20	10	30
10th	10	40	20	40
25th	40	70	50	50
50th	70	100	100	100
75th	90			
90th	100			
95th				
100th				

Summary and Descriptive Statistics

Females and Males Combined

The means, standard deviations, and coefficients of variation for all varibles measured in females and males combined have been presented in Table 5. As a rather preliminary observation, it was interesting to note that, although measured in different systems, chronological age, dental age, and skeletal age exhibited similar standard deviations and coefficients of variation but

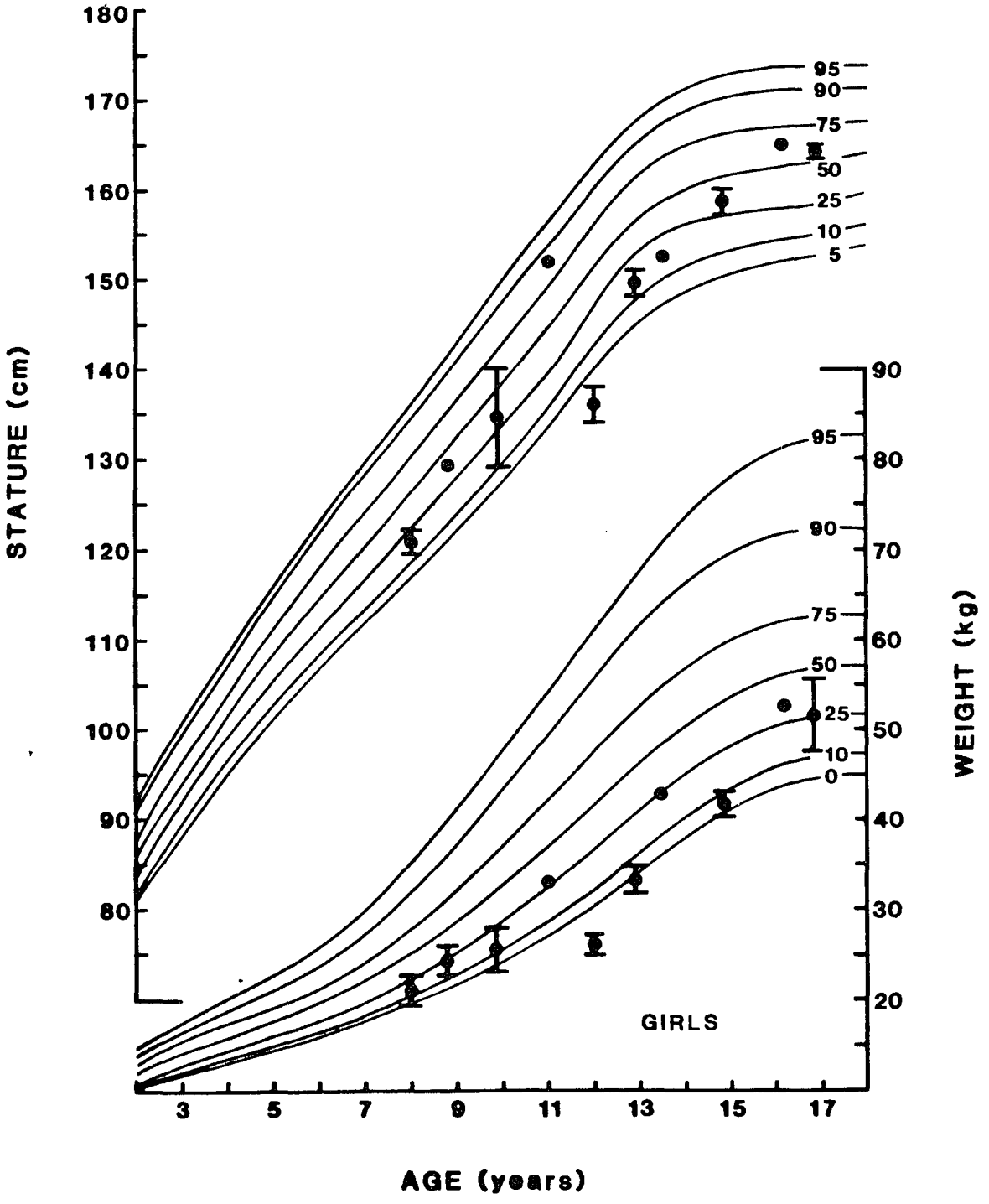

Fig. 1. CF study females: age class means and standard errors for height and weight plotted against NCHS centiles.

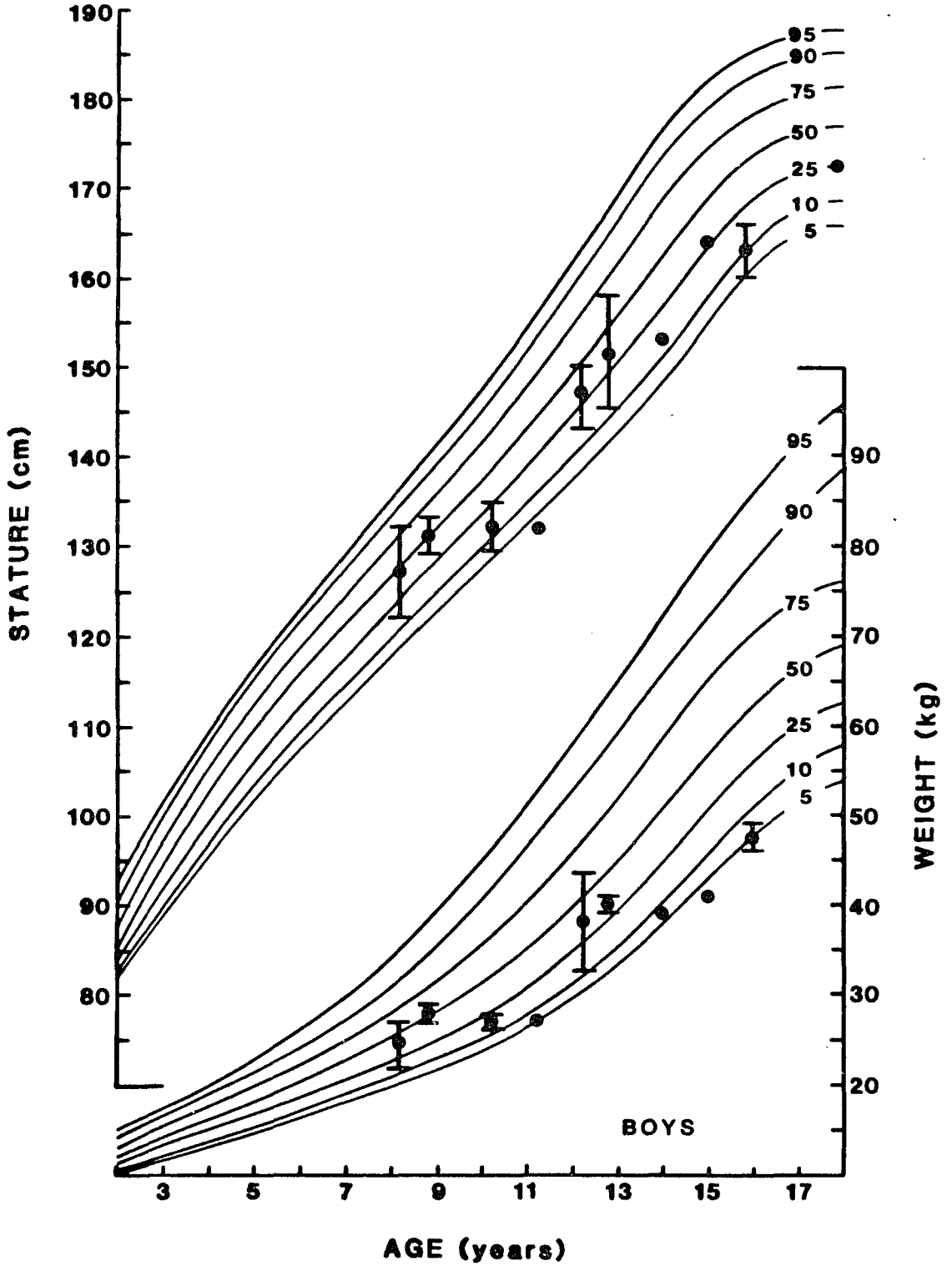

Fig. 2. CF study males: age class means and standard errors for height and weight plotted against NCHS centiles.

differed in their means. The mean sexual maturity score of 1.0 (out of 4.0 possible points) was consistent with a mean age of between the values obtained for mean CF age (10.4 years) and mean chronological age (12.4 years).

TABLE 5

BOTH SEXES COMBINED: SUMMARY STATISTICS FOR VARIABLES IN CF STUDY

Variables	Mean	Standard Deviation	Coefficient of Variation
Chronological age	12.4	3.0	0.239
CF age	10.4	3.2	0.307
Age at diagnosis	2.0	2.5	1.215
Pulmonary score	14.8	10.1	0.683
Dental maturity score	89.6	11.7	0.131
Dental age	11.8	3.1	0.265
Skeletal maturity score	757.0	191.2	0.252
Skeletal age	11.5	3.1	0.266
Sexual maturity score	1.0	1.2	1.248

Inspection of the correlation matrix for the study sample (Table 6) revealed some associations which were tentatively supportive of the general hypothesis. Correlations between the pulmonary disease severity score and dental age, skeletal age, and sexual maturity were low and, by virtue of the t-test, insignificant at the 0.01 level. All developmental indicators were significantly associated with one another, with chronological age, and with CF age (i.e., years since diagnosis).

TABLE 6

BOTH SEXES COMBINED: CORRELATION MATRIX FOR VARIABLES IN CF STUDY

	CA	CFA	DxA	Pul	Den	SA	SMS
Chronological age (CA)	1.00						
CF age (CFA)	0.68*	1.00					
Diagnosis age (DxA)	0.32	-0.47*	1.00				
Pulmonary score (Pul)	0.24	0.31	-0.11	1.00			
Dental age (Den)	0.93*	0.68*	0.24	0.25	1.00		
Skeletal age (SA)	0.95*	0.63*	0.33	0.22	0.90*	1.00	
Sexual maturity score (SMS)	0.86*	0.48*	0.42*	0.06	0.77*	0.83*	1.00

*$p < 0.01$.

The Female Sample

Summary statistics for the variables measured on the female subjects are presented in Table 7. Female means are very close to those for the combined sex sample with slightly higher values in the pulmonary disease severity score (15.6) and sexual maturity score (1.1). Indications of dispersion of values from the means (standard deviations) and relative variability within the measures (coefficients of variation) were also nearly identical to those parameters for the larger sample.

The correlation matrix for the female sample's variables displayed patterns of association much like

TABLE 7

CF STUDY FEMALES: SUMMARY STATISTICS FOR VARIABLES

Variable	Mean	Standard Deviation	Coefficient of Variation
Chronological age	12.4	3.1	0.248
CF age	10.5	3.3	0.321
Age at diagnosis	1.9	2.4	1.269
Pulmonary score	15.6	8.1	0.522
Dental maturity score	89.9	11.7	0.130
Dental age	11.5	3.2	0.273
Skeletal maturity score	806.9	185.3	0.230
Skeletal age	11.3	3.1	0.275
Sexual maturity score	1.1	1.4	1.249

those in the matrix for combined sexes (see Table 8). Low and insignificant correlations between the developmental variables and disease severity, as measured by the method of Taussig et al. (1973), were obtained. Again, significant associations among the three maturational indicators and between them and both chronological and CF age variables were seen. Mean values for all variables per age class have been reported for the female subjects in Table 9.

The Male Sample

The contribution to the variable parameters of the sample by the males in this study was roughly equivalent to that by the females (see Table 10). Notable

TABLE 8

CF STUDY FEMALES: CORRELATION MATRIX FOR VARIABLES

	CA	CFA	DxA	Pul	Den	SA	SMS
Chronological age (CA)	1.00						
CF age (CFA)	0.72*	1.00					
Diagnosis age (DxA)	0.27	-0.48	1.00				
Pulmonary score (Pul)	-0.19	-0.18	1.12	1.00			
Dental age (Den)	0.93*	0.73*	0.17	-0.27	1.00		
Skeletal age (SA)	0.96*	0.70*	0.25	-0.17	0.89*	1.00	
Sexual maturity score (SMS)	0.88*	0.63*	0.24	-0.33	0.78*	0.88*	1.00

*$p < 0.01$.

TABLE 9

CF STUDY FEMALES: VARIABLE MEANS PER AGE CLASS

Age Class	Chronological Age	CF Age	Age at Diagnosis	Pulmonary Score	Dental Score	Dental Age	Skeletal Score	Skeletal Age	Sexual Maturation Score
8	8.1	7.3	0.4	16.7	66.9	7.5	552.3	7.6	0.0
9	9.0	7.4	1.6	13.7	78.4	7.9	533.7	7.3	0.0
10	10.3	7.2	3.1	38.0	85.9	8.7	667.0	9.1	0.0
11	10.9	8.6	2.3	12.5	88.9	9.5	784.0	10.3	0.0
12	11.8	11.3	0.6	16.0	94.8	11.4	840.5	11.0	0.4
13	12.9	11.5	1.5	19.5	97.4	13.2	895.0	12.0	0.8
14	14.2	10.0	4.2	14.0	95.8	11.7	939.0	12.9	2.2
15	15.1	12.3	2.8	7.0	99.2	15.0	968.0	13.7	1.9
16	15.9	14.6	1.3	10.0	100.0	16.0	990.0	14.6	3.5
17	17.3	14.7	2.6	14.0	99.7	15.6	1000.0	16.0	3.4

exceptions were in the mean pulmonary disease severity score which was 1.5 points lower and in the mean sexual maturity score which was 18 percent lower than in females. Although the males exhibited the same mean age (12.4 years) as the females, their skeletal and dental age means were relatively, but not significantly (see Sproul & Huang, 1964, p. 668), advanced over those for the female sample.

TABLE 10

CF STUDY MALES: SUMMARY STATISTICS FOR VARIABLES

Variable	Mean	Standard Deviation	Coefficient of Variation
Chronological age	12.4	2.9	0.236
CF age	10.2	3.1	0.300
Age at diagnosis	2.1	2.5	1.194
Pulmonary score	14.1	11.7	0.822
Dental maturity score	89.3	11.9	0.134
Dental age	12.0	3.1	0.262
Skeletal maturity score	715.1	189.2	0.265
Skeletal age	11.7	3.1	0.265
Sexual maturity score	0.9	1.1	1.252

The patterns of association between the variables were viewed in the matrix of correlations presented in Table 11. They were the same as those for the female and combined samples with an interesting difference. A moderate, but significant, positive correlation between

dental age and pulmonary disease severity was observed in the males. Neither of the other maturational indicators, usually considered more sensitive to disease stessors, displayed this sort of association. Additionally, the males exhibited a significant correlation between sexual maturity, as indicated on a 4-point scale, and age at diagnosis which also was not observed for the other sex. Male age-class variable means have been reported in Table 12.

TABLE 11

CF STUDY MALES: CORRELATION MATRIX FOR VARIABLES

	CA	CFA	DxA	Pul	Den	SA	SMS
Chronological age (CA)	1.00						
CF age (CFA)	0.65*	1.00					
Diagnosis age (DxA)	0.37	-0.47	1.00				
Pulmonary score (Pul)	0.52*	0.64*	-0.18	1.00			
Dental age (Den)	0.94*	0.64*	0.30	0.58*	1.00		
Skeletal age (SA)	0.95*	0.59*	0.38	0.46	0.90*	1.00	
Sexual maturity score (SMS)	0.86*	0.31	0.62*	0.34	0.79*	0.89*	1.00

*$p < 0.01$.

TABLE 12

CF STUDY MALES: VARIABLE MEANS PER AGE CLASS

Age Class	Chrono-logical Age	CF Age	Age at Diag-nosis	Pulmo-nary Score	Dental Score	Dental Age	Skele-tal Score	Skele-tal Age	Sexual Matura-tion Score
8	8.1	5.6	2.5	8.7	67.7	7.8	436.0	7.3	0.0
9	8.8	7.2	1.6	7.0	72.6	8.1	483.7	8.1	0.0
10	10.3	9.9	0.4	2.0	89.8	10.3	593.0	9.8	0.0
11	10.9	10.5	0.4	13.3	87.8	10.0	618.0	10.1	0.0
12	12.0	11.7	0.3	11.0	95.2	12.9	744.7	11.9	0.2
13	12.8	9.5	3.2	15.3	92.7	11.3	768.0	12.3	0.7
14	13.8	12.6	1.3	7.5	94.9	12.7	680.0	12.5	1.7
15	15.4	14.3	1.1	33.4	98.7	15.7	859.6	13.9	1.6
16	15.9	10.3	5.6	21.7	100.0	16.0	955.7	15.6	2.7
17	17.0	12.0	5.0	16.5	99.0	15.8	982.5	16.9	2.9

Developmental Indicators

Dental Development

Mean dental maturity scores and dental ages per age class were given for females (Table 9) and males (Table 12). A comparison of these mean cross-sectional values with the developmental standard centile distribution in Demirjian et al. (1973) and Demirjian (1978) suggested that dental maturation was indeed delayed in these two groups. One hundred percent of both females and males were determined to be at or below the 50th centile for dental development (Table 13). The female sample appeared to be relatively more behind for this system than did the males, as 80 percent of the female means were at or below

the 10th centile line compared to 40 percent for the male sample. This was expressed in graphic form in Figure 3 for females and Figure 4 for males.

TABLE 13

PERCENT OF MEAN CROSS-SECTIONAL DENTAL MATURITY SCORES AT OR BELOW STANDARD PERCENTILES (DEMIRJIAN, 1978) FOR FEMALES AND MALES WITH CF IN THIS STUDY

Percentile	Females	Males
3rd	10	20
10th	80	40
50th	100	100
90th	100	100
97th	100	100
100th	100	100

The mean dental maturity scores for the female age classes displayed a consistency of centile position with time, as scores remained between the 10th and 3rd centile from 8 to approximately 13 years of age. A drop below the 3rd centile occurred between 13 and 15 years of age; perhaps in association with the increased sexual maturational activity or the above-average pulmonary disease severity score evidenced in Table 9. A similar pattern was observed for the males (Figure 4). In their case, mean dental maturity scores plotted between the 50th and 10th centile curves up to 12 years of age where they dropped to the 3rd centile for two age intervals. Examination of the cross-sectional variable means for males

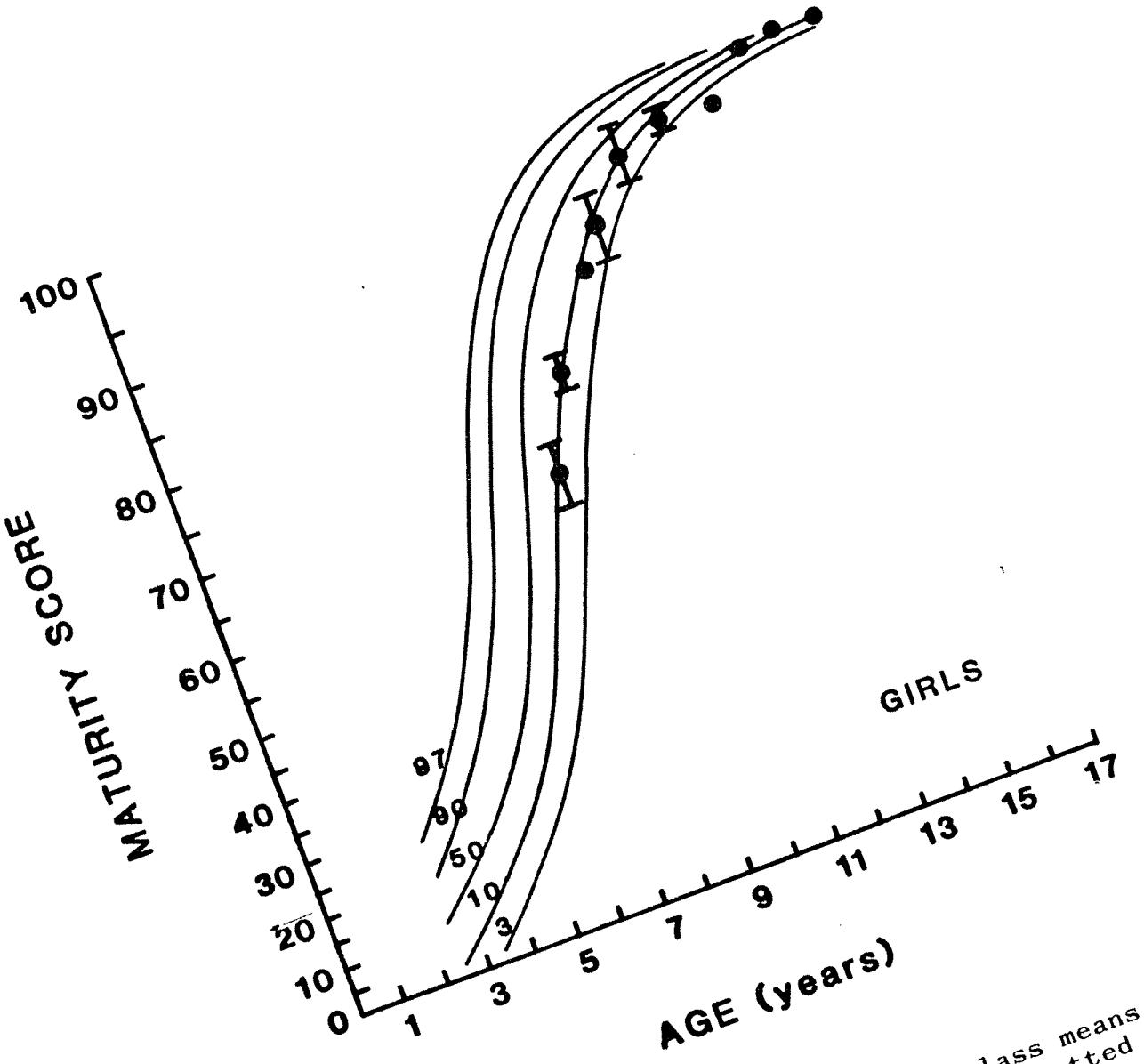

Fig. 3. CF study females: age class means and standard errors for dental maturity scores plotted against French-Canadian centiles.

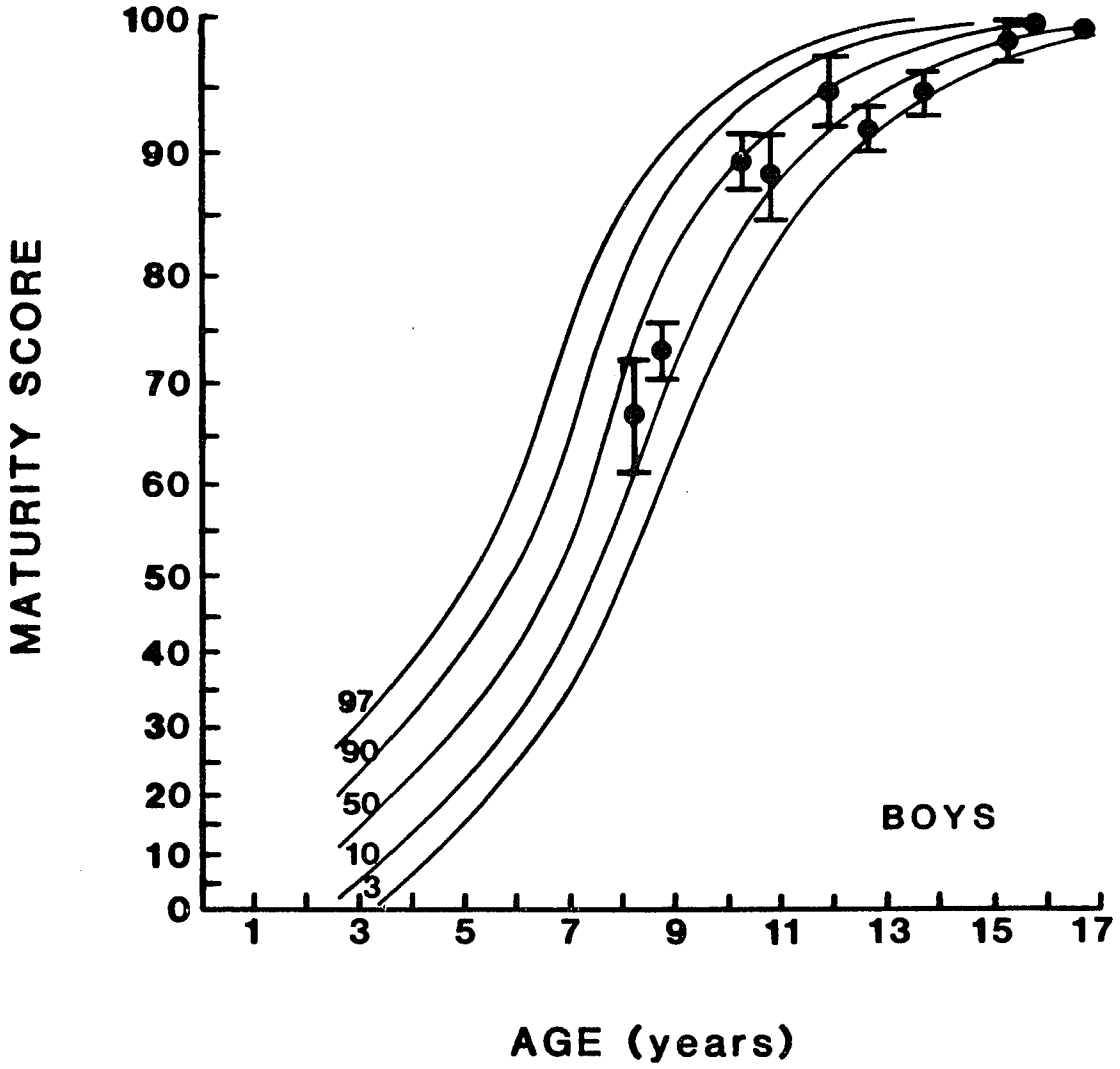

Fig. 4. CF study males: age class means and standard errors for dental maturity scores plotted against French-Canadian centiles.

in Table 12 yielded the somewhat equivocal impression that sexual maturation was involved. However, pulmonary disease scores were also seen to waver about and above the group mean during the 13- to 16-year age intervals.

Skeletal Development

Age class means for the TW2 20 bone maturity scores and associated skeletal ages were presented in Table 9 for females and in Table 12 for males. As with dental maturation, both the females and the males in this study showed consistent delays in cross-sectionally viewed skeletal development (see Table 14). One hundred percent of the age-class means for skeletal maturity scores were at or below the 50th centile curve in both females and males. Females again displayed proportionately greater delay with 70 percent of their age-class means at or below the 10th centile compared to 20 percent for males.

Mean age-class scores were plotted against the standard centile curves produced by Tanner et al. (1975). This has been illustrated in Figure 5 for female age-classes and Figure 6 for males. Just as was observed for the dental maturity scores, male mean skeletal scores were maintained between the 50th and 25th centiles until approximately age 12, when they dipped between the 10th and 3rd centiles for two age intervals. The female skeletal maturity picture was somewhat different. Although

TABLE 14

PERCENT OF MEAN CROSS-SECTIONAL SKELETAL MATURITY SCORES AT OR BELOW STANDARD PERCENTILES (TANNER ET AL., 1975) FOR FEMALES AND MALES WITH CF IN THIS STUDY

Percentile	Females	Males
3rd	0	0
10th	70	20
25th	90	70
50th	100	100
75th	100	100
90th	100	100
97th	100	100
100th	100	100

always below the 50th centile, their age-class means traveled back and forth across centile lines until approximately age-class 14 where they were stabilized between the 10th and 3rd centiles until adulthood. From a visual inspection of Table 9 and Table 8, no immediate explanation was forthcoming for this pattern.

Sexual Development

Mean scores for sexual maturation were presented by age intervals for females in Table 9 and for males in Table 12. In both sex samples the first evidence of sexual development was visible in the 12-year-old class. For the female sample, this translated to one 11.6-year-old female subject who had attained the initial maturational stages in breast, pubic hair, and axillary hair

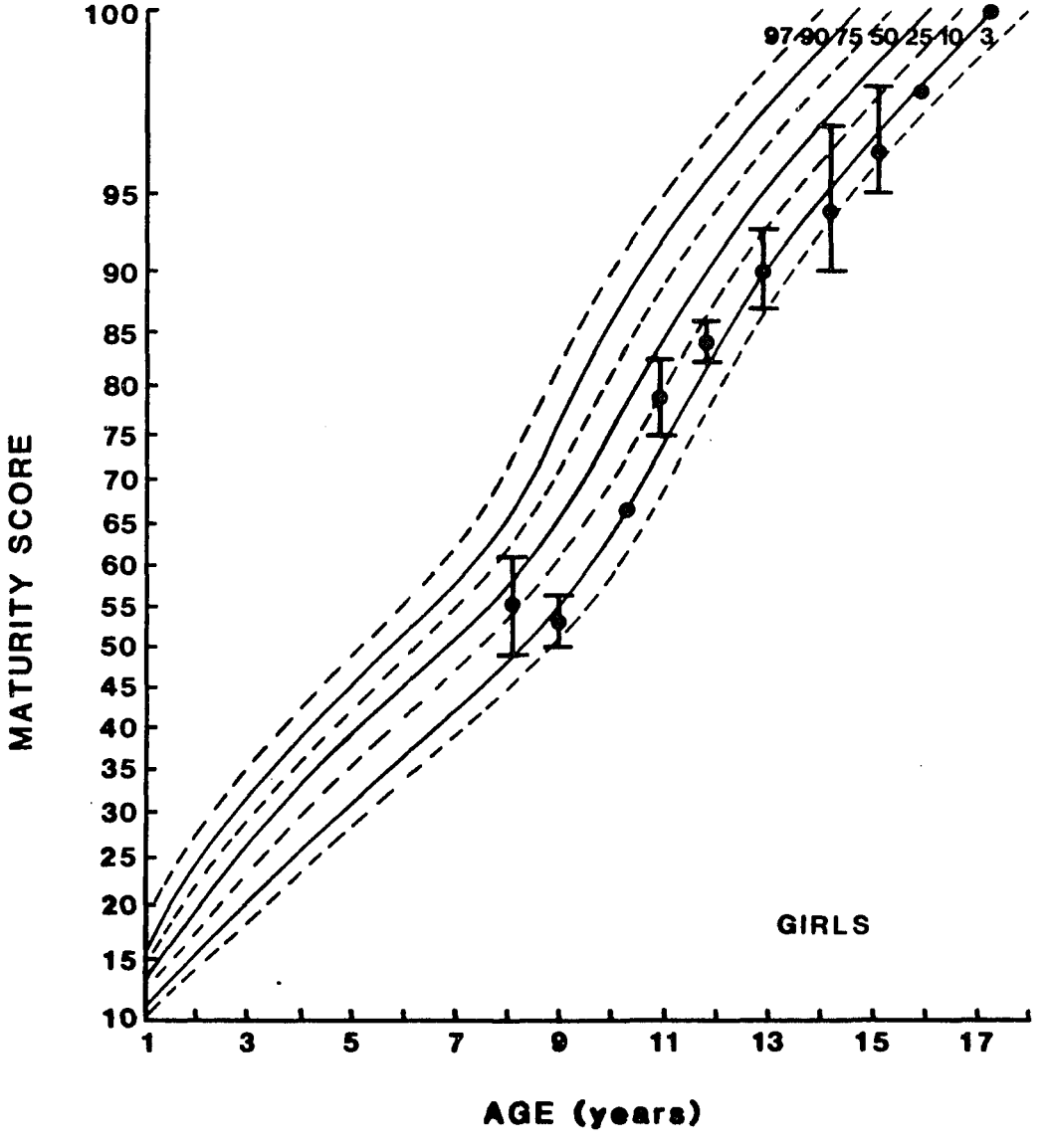

Fig. 5. CF study females: age class means and standard errors for TW2 20 bone maturity scores plotted against British centiles.

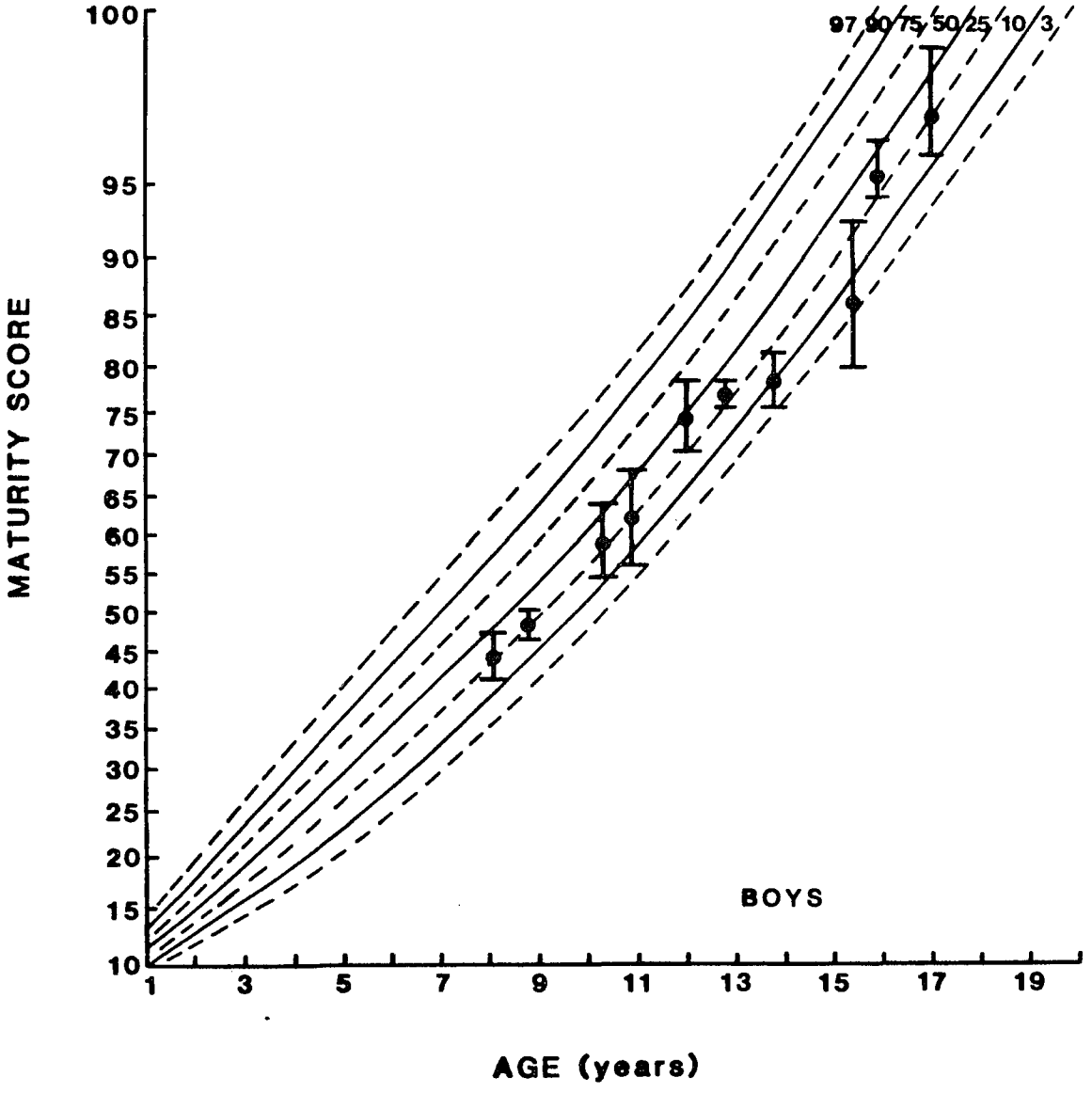

Fig. 6. CF study males: age class mean and standard errors for TW2 20 bone maturity scores plotted against British centiles.

development ($B2^+$, $P2^+$, and $H2^+$ respectively), but had not yet experienced menarche. In the male sample, this mean score reflected the attainment of first-stage development of the external genitalia ($G2^+$) and pubic hair ($P2^+$) but no visible axillary hair in an 11.9-year-old subject. From the 12-year age interval onward the proportion of females and males who had experienced sexual maturational changes in the secondary sex characters increased at a steady rate. On the basis of average scores in Tables 9 and 12 females may appear to have been only slightly ahead of the males until the 14-year age class when the distance increased dramatically. This represented the somewhat delayed menarche evidenced in these females. With the appearance of menarche scores on the data sheets there was a concomitant jump in breast, pubic hair, and axillary hair development. With one exception, no female who had experienced menarche was at or below breast development stage 2. In females who had experienced menarche, there was a greater degree of concordance among the developing secondary sex characters compared with those who had not. The oldest females were relatively more sexually mature than their age-class male counterparts.

When viewed in a similar way, the mean male sexual development data in Table 12 accurately reflected the steady rates of change observed in the original data. For the male sample, no "jumping-over" stage 2

development, as was apparently evidenced in the female cross-sectional sample, was observed. Individual male sexual development, although slow, consistently displayed concordance among the developmental stages of the characters.

Sexual development was somewhat behind that for standard populations in both the females and males in this study. In Figure 7 individuals of given ages who had attained a particular maturational stage when examined were plotted against centiles for sexual development established in Tanner (1962, 1978). In these status quo type plots, the majority of individuals who had achieved a specific level of breast, pubic hair, or external genital development had either done so later than 50 percent of the standards or had failed to mature to the next stage as quickly as 50 to 97 percent of the standard population.

Regression Analyses

Appraisal of the correlation matrices for the original variables (Tables 6, 8, and 11) disclosed consistently high and significant correlations among the maturational indicators. By means of principal components analysis the matrix containing the variables of dental age, skeletal age, and sexual maturation score were decomposed into three independent composite vectors, or principal components, to be used as independent variables in

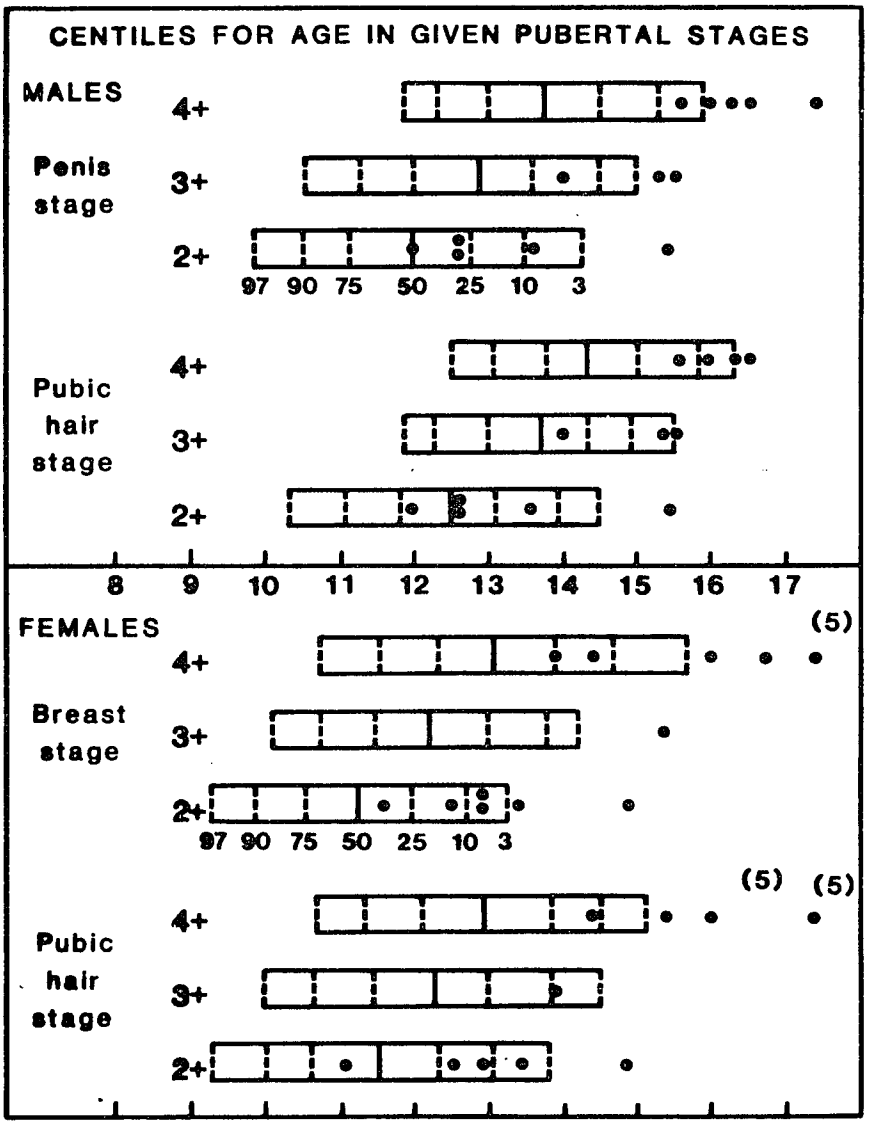

Fig. 7. CF study females and males: ages at attainment of pubertal stages compared to British centiles.

regression analyses. This was done for the data from the female and male samples. Subsequently, multiple linear regressions were performed with BMDP4R (Dixon et al., 1981) with chronological age and pulmonary disease severity score as the dependent variables. In these analyses, the results of which will be reported below, the first principal component explained such a substantial proportion of the variance in the original data sets (90 percent for females; 89 percent for males) that it alone served as a "biological age" variable in the analyses. In addition, the variable of CF age, originally considered in the hypotheses, was not utilized as a dependent variable even though it was significantly associated with the maturational indicators. It was determined to be too similar to chronological age, due to very low mean ages at diagnosis, to be of any use. Age at diagnosis, the variable of interest in the acclimatization hypothesis, was the last dependent variable examined, although it did not show significant correlations with the developmental variables in the preliminary analyses.

The Female Sample

Information pertinent to the regression of chronological age on the principal components for the female maturational indicators has been presented in Figure 8. Supporting the first principal component's (PCI)

appellation of biological age component were its measure of correlation with chronological age (0.97) and its very high R^2 value (0.95), an indicator of the amount of the variance explained in the first step of the multiple linear regression. Observed in vacuo, the results of this analysis were not too informative; however, reference to Figure 9 placed them in perspective.

In Figure 9 the salient features for the regression of pulmonary disease score on the biological age component, and the second and third principal components have been presented. These results were in sharp contrast to those for the previous regression. A negative and insignificant correlation was obtained between PCI and the disease score. The R^2 for the regression was a nonsignificant 0.07 for PCI, 0.23 for PCII (+PCI), and 0.24 for PCIII (+PCI+PCII). Consequently, the variance explained by the regression of disease severity on biological age was very low. The regression of age at diagnosis on these same three components yielded even lower nonsignificant correlations and R^2 values in the female sample (Figure 10).

The Male Subjects

The results of the regressions on principal components of the data from the male sample were not so unequivocal. The regression of chronological age on the

Total Sum of Squares: 207.16

Degrees of Freedom: 22

Mean Square: 9.42

Correlation between Principal Components (PC) and Chronological Age

PCI	PCII	PCIII
0.97	-0.08	-0.07

Regression Coefficients of Principal Components

Constant ($\bar{Y}$)	PCI	PCII	PCIII
12.38	1.81	-0.53	-0.74

Coefficients of Variables Obtained from Regression on Principal Components

	Residual Sum of Squares	F-Values	R^2	Constant	Variables: Dental Age	Variables: Skeletal Age	Variables: Sexual Scores
PCI:	11.18	368.25	0.95	3.82	0.33	0.35	0.75
PCII:	9.82	200.86	0.95	2.72	0.44	0.35	0.47
PCIII:	8.87	141.54	0.96	1.97	0.34	0.55	0.26

Cumulative Proportion of Total Variance of Independent Variables (Principal Components)

PCI	PCII	PCIII
0.90	0.97	1.00

Fig. 8. CF study females: regression of chronological age on principal components of 3 developmental indicators (dental age, skeletal age, and sexual maturity score).

Total Sum of Squares: 1451.65

Degrees of Freedom: 22

Mean Square: 65.98

Correlation between Principal Components (PC) and Disease Severity Score

PCI	PCII	PCIII
-0.27	-0.10	-0.40

Regression Coefficients of Principal Components

Constant ($\bar{Y}$)	PCI	PCII	PCIII
15.54	-1.32	-1.66	-11.72

Coefficients of Variables Obtained from Regression on Principal Components

	Residual Sum of Squares	F-Values	R^2	Constant	Variables: Dental Age	Skeletal Age	Sexual Scores
PCI:	1109.71	3.08	0.07	9.86	-1.89	2.81	-3.88
PCII:	1096.52	2.05	0.23	6.46	-1.52	2.83	-4.75
PCIII:	1213.61	4.12	0.24	3.63	-1.65	3.06	-3.34

Cumulative Proportion of Total Variance of Independent Variables (Principal Components)

PCI	PCII	PCIII
0.90	0.97	1.00

Fig. 9. CF study females: regression of disease severity on principal components of 3 developmental indicators (dental age, skeletal age, and sexual maturity score).

Total Sum of Squares: 128.52

Degrees of Freedom: 22

Mean Square: 5.84

Correlation between Principal Components (PC) and Age at Diagnosis

PCI	PCII	PCIII
0.23	0.11	-0.12

Regression Coefficients of Principal Components

Constant ($\bar{Y}$)	PCI	PCII	PCIII
1.90	0.34	0.56	-1.05

Coefficients of Variables Obtained from Regression on Principal Components

					Variables		
	Residual Sum of Squares	F-Values	R^2	Constant	Dental Age	Skeletal Age	Sexual Scores
PCI:	121.59	1.20	0.05	0.29	0.06	0.07	0.14
PCII:	118.17	0.55	0.06	0.38	-0.21	0.33	0.14
PCIII:	119.69	0.74	0.08	-0.77	-0.09	0.34	-0.16

Cumulative Proportion of Total Variance of Independent Variables (Principal Components)

PCI	PCII	PCIII
0.90	0.97	1.00

Fig. 10. CF study females: regression of age at diagnosis on principal components of 3 developmental indicators (dental age, skeletal age, and sexual maturity score).

biological age component yielded coefficients totally consistent with those from the same regression with the female data; for example, the regression correlation for PCI = 0.97 and R^2 for PCI = 0.94 (see Figure 11). However, perusal of the material presented in Figure 12 uncovers a possibly different scenario (augured by the correlation in Table 11?). The regression of pulmonary disease severity score on the principal components of the developmental indicators produced moderate correlation with PCI (0.49) and an R^2 value (for PCI) of a similar magnitude (0.24). This was certainly not a relationship of the degree seen for chronological age; but, it was different enough from that reported in females to attract attention. However, as tested by the method detailed in Sokal and Rohlf (1982, pp. 634-638) with reference to Snedecor's table in Rohlf and Sokal (1981, pp. 167-168), the R^2 value was demonstrated to be nonsignificant at the 0.01 level. Similarly, regression of age at diagnosis on the male biological age component did result in a moderate, but nonsignificant, multiple R^2 value (Figure 13).

Summary

Observations made on the data collected and results of the statistical analyses conducted on those data were presented in textual, tabular, and graphic formats. The preliminary analysis of clinically derived growth

Total Sum of Squares: 222.24

Degrees of Freedom: 26

Mean Square: 8.55

Correlation between Principal Components (PC) and Chronological Age

PCI	PCII	PCIII
0.97	-0.07	-0.027

Regression Coefficients of Principal Components

Constant ($\bar{Y}$)	PCI	PCII	PCIII
12.37	1.73	-0.42	-0.15

Coefficients of Variables Obtained from Regression on Principal Components

	Residual Sum of Squares	F-Values	R^2	Constant	Variables: Dental Age	Variables: Skeletal Age	Variables: Sexual Scores
PCI:	12.77	409.98	0.94	3.87	0.32	0.33	0.86
PCII:	11.71	215.75	0.95	2.88	0.39	0.37	0.55
PCIII:	11.65	138.57	0.95	2.85	0.35	0.41	0.54

Cumulative Proportion of Total Variance of Independent Variables (Principal Components)

PCI	PCII	PCIII
0.89	0.97	1.00

Fig. 11. CF study males: regression of chronological age on principal components of 3 developmental indicators (dental age, skeletal age, and sexual maturity score).

Total Sum of Squares: 3556.66

Degrees of Freedom: 26

Mean Square: 136.79

Correlation between Principal Components (PC) and Disease Severity Score

PCI	PCII	PCIII
0.49	-0.29	0.23

Regression Coefficients of Principal Components

Constant ($\bar{Y}$)	PCI	PCII	PCIII
14.22	3.48	-7.20	8.72

Coefficients of Variables Obtained from Regression on Principal Components

	Residual Sum of Squares	F-Values	R^2	Constant	Variables: Dental Age	Variables: Skeletal Age	Variables: Sexual Scores
PCI:	2715.97	7.74	0.24	-2.80	0.65	0.66	1.73
PCII:	2406.70	5.73	0.32	-19.75	1.70	1.44	-3.52
PCIII:	2213.87	4.65	0.38	-18.47	3.57	-0.63	-2.97

Cumulative Proportion of Total Variance of Independent Variables (Principal Components)

PCI	PCII	PCIII
0.89	0.97	1.00

Fig. 12. CF study males: regression of disease severity on principal components of 3 developmental indicators (dental age, skeletal age, and sexual maturity score).

Total Sum of Squares: 165.67

Degrees of Freedom: 26

Mean Square: 6.37

Correlation between Principal Components (PC) and Age at Diagnosis

PCI	PCII	PCIII
0.46	0.51	-0.11

Regression Coefficients of Principal Components

Constant ($\bar{Y}$)	PCI	PCII	PCIII
2.11	0.71	2.67	-0.88

Coefficients of Variables Obtained from Regression on Principal Components

	Residual Sum of Squares	F-Values	R^2	Constant	Variables: Dental Age	Variables: Skeletal Age	Variables: Sexual Scores
PCI:	88.26	10.52	0.21	4.94	-0.26	-0.16	2.30
PCII:	123.11	8.64	0.46	8.40	-0.39	-0.29	1.95
PCIII:	86.30	7.05	0.48	4.80	-0.45	0.05	2.24

Cumulative Proportion of Total Variance of Independent Variables (Principal Components)

PCI	PCII	PCIII
0.89	0.97	1.00

Fig. 13. CF study males: regression of age at diagnosis on principal components of 3 developmental indicators (dental age, skeletal age, and sexual maturity score).

metrics indicating the existence of growth delays in the clinical population from which the subjects came was detailed. Summary statistics were presented for all variables measured on combined sex, female, and male subject groups. These suggested, among other things, significant associations among dental, skeletal, and sexual development and between the developmental indicators and chronological age. Noticeably absent, with one exception, were significant correlations with disease severity. A review of the cross-sectional data for dental, skeletal, and sexual development indicated measurable delays for all three in both sexes. The results of regression of pulmonary disease score and chronological age on the biological age component in both females and males indicated a closer and significant relationship existed between the developmental component and chronological age than between this component and pulmonary disease severity.

CHAPTER IV

DISCUSSION AND CONCLUSIONS

At the outset, the acknowledged goals of this study could be partitioned into two different classes; one of which contained the more substantive aims, and another consisting of less tangible objectives. The substantive aims of the research included the elucidation of the patterns of relationship among maturational indicators in CF and the testing of the general hypothesis that delayed development observed in CF was a functionally adaptive, rather than pathological, response to that inherited disorder. The second category of objectives included the desire to apply principles from the study of human variation and evolution to a problem in clinical auxology and, by so doing, to demonstrate the utility of that approach for answering proximate ontogenetic questions. The accomplishment of the more substantive goals was reported in the preceding chapter. In the discussion of those results it is hoped that the attainment of the latter, less concrete objectives will be evidenced also.

Functional Adaptation in Chronic Disease

The suggestion that a variant pattern of development may have phylogenetic implications is not new to biological anthropology. Both interspecific and interpopulational differences have been attributed to various ontogenetic modifications. Likewise, to suggest that a particular developmental pattern could be an adaptation, either functional or genetic, would not be objectionable, in principle at least, to most biological anthropologists. However, the hypothesis that a developmental phenotype is a functional adaptation to an inherited disorder may be considered somewhat unorthodox as it suggests a response to endogenous, rather than exogenous environmental factors. Previous research into functional adaptation has focused on interactions between the organism and its external environment. However, this research has been predicated on the contention that an inherited chronic disorder could establish an infra-organismal environment with which the individual could interact in a functionally adaptive manner.

Functional Adaptation in Cystic Fibrosis

On the whole, the analyses of the developmental data in this sample verify that dental, skeletal, and sexual maturation are indeed delayed in cystic fibrosis.

The apparent coordination among these different developmental systems and the refutation of the pathological hypothesis indicates functional adaptation. In light of the failure of the acclimatizational hypothesis to hold, the more tenable of the adaptive explanations is the genetic alternative. This is to say that the pattern of delayed development observed in this sample was not demonstrated to have been affected by the variables heretofore most widely accepted as being responsible for retardation (or lack thereof) in cystic fibrosis: disease severity and age at diagnosis. As these were measures of the most biomedically significant environmental (internal and external, respectively) stressors for growing individuals with this disorder, the evidence supports the attribution of the observed delays to a genetic influence. This does not suggest that CF development is immutable or impervious to the effects of disease stress or amount of therapeutic intervention. Rather, it implies that the developmental norms of reaction on which these variables impinge are different from those of the nonafflicted members of the standard populations.

As a functional adaptation it is hypothesized that this developmental phenotype contributes to the maintenance of physiological homeostasis; increasing the probability of survival in much the same ways as the functionally adaptive responses postulated for growing individuals

in some Andean populations (Frisancho, 1981; Moore & Regensteiner, 1983). The modifications of developmental rates observed in those high altitude dwellers have been suggested to ameliorate the effects of high altitude hypoxia, which include increased oxygen work of breathing and secondary malnutrition (Frisancho, 1981). This accommodation is likely the result of genetic differences in developmental regulation which have the beneficial effect of diminishing growth energies required per unit of time by lengthening the postnatal growth period (Beall et al., 1977; Moore & Regensteiner, 1983). It is proposed that a CF developmental phenotype, identified in this study, acts in an analogous fashion to facilitate the achievement of nearly optimal auxologic progress in the face of low-grade chronic hypoxemia, increased oxygen work of breathing, infection, maldigestion, and malabsorption. It is also postulated that some of the clinically observed delay in height gain is attributable to the overall pattern of functionally adaptive developmental retardation. The observation that normal adult stature is approximated in CF patients surviving to adulthood (Green, 1983) is analogous to the high altitude South American situation and is considered supportive of this conclusion.

However, it is not so likely that this proposition of adaptive delay extends to growth in weight and adiposity to the same degree. Although not directly

considered in this research, the reports on growth in these parameters for CF and the high altitude analog suggest a greater environmental than genetic contribution. Kraemer et al. (1978), Kreissl et al. (1972), and Sproul and Huang (1964) have all reported a very high correlation between weight and severity of disease in CF, even though they were not in agreement concerning their other findings. Body composition studies in infants and older subjects with CF suggest a similar relationship for fat deposition (Lloyd-Still, 1983a, 1976; Forbes, Schwartz & Nelson, 1979; Moshang & Holsclaw, 1980). In the high altitude situation, growth in these parameters, which contributes to mass and shape differences, has been attributed primarily to developmental acclimatization and environmental stress, rather than genetic influences (Frisancho, 1981; Haas et al., 1982). In both CF and the high altitude scenarios, reduction of the stress, or therapeutic intervention, has resulted in dramatic changes in these parameters without so greatly affecting linear or maturational velocities (Moore & Regensteiner, 1983; Moshang & Holsclaw, 1980).

Although the pattern of development elucidated for individuals with CF in this study may be considered a functional adaptation and predominantly under the influence of genetic factors, it cannot be said to fulfill the more strict requirements for a genetic adaptation

resulting from natural selection. The criterion of heritability may be met, as may that for functional advantage in association with an environmental stress. One might easily argue that delayed development, because it does achieve the functions postulated above, increases the probability that those who exhibit it will survive to adulthood in contrast to those who do not. However, natural selection is differential fertility, not differential mortality. Decreased mortality, in association with a particular phenotypic character, is a necessary condition of adaptation only insofar as it allows for reproductive opportunities to be realized should they arise. However, it is not the sufficient condition for genetic adaptation; positive differential fertility is.

In view of the evidence for reproductive success in CF homozygotes, one is hard pressed to advance a natural selection argument for their delayed maturation. Sterility in the majority of CF males was confirmed by Denning, Sommers & Quigley (1968) and Kaplan et al. (1968). Although normal semen analyses have been reported for a few males (Taussig et al., 1972), structural anomalies which contribute to the production of aspermatic ejaculate have precluded fertility in all but an estimated 2 percent of the postpubertal males with CF. CF females do not exhibit the same degree of difficulty with fertility as males. No major anatomical impediments to

fertility have been noted for them; however, the mucosal cap of the uterine cervix has been suggested to be somewhat more resistant to removal than that found in non-CF females. Yet a number of pregnancies have been reported for females with CF. In one survey 70 female homozygotes were reported to have experienced 100 pregnancies in which 46 produced viable offspring, only one of which was diagnosed as having CF (Wood, Boat & Doershuk, 1976, p. 847). These data, although not as depressing as some anecdotal information concerning the disorder, are not especially suggestive of natural selection (i.e., differential fertility) in females and would seem to obviate even the consideration of it for the males.

If, however, it could be demonstrated that there exists phenotypic heterogeneity in CF developmental patterns and that females who exhibit delayed development do experience decreased mortality and increased fertility compared to those who do not, the natural selection argument would acquire some impetus. Such is not the case at this time. The results of this study do not facilitate an inference of historical genesis from a developmental variant which may have current utility. These sorts of distinctions are not supportable with the presently available data. Consequently, the label of functional adaptation may be applied more appropriately to the pattern of development observed in this research.

Clinical Implications

If, in fact, the observed pattern of delayed development in these CF patients is more reflective of genetic than environmental influences, changes in one clinical monitoring and evaluation method may be indicated. Growth standards, derived from large-scale longitudinal surveys of individuals not afflicted with CF (e.g., Hammill et al., 1979), are normally employed by pediatricians to evaluate the physical growth of their patients. Comparison with these standards may provide the clinician with a means of retrospectively examining the impact of past experiences and the efficacy of previous therapeutic interventions in terms of the patient's growth. Additionally, the percentile ranking, corresponding to the patient's growth metrics, may be a decisive factor toward the corroboration of a specific diagnosis. Given the results of this study such comparisons may be inappropriate where CF patients are concerned.

If the maturational delay observed in dental, skeletal, and sexual systems does signal the existence of a developmental norm of reaction typical of individuals with CF, then growth rates for metric indicators, usually measured by clinicians, may exhibit concomitant delays. If that is the case, comparisons of CF individuals to normative standards would yield misleading and possibly disappointing results. This disappointment would be

unwarranted if, as in the example of the high altitude dwellers, the data were actually descriptive of normally slow, functionally adaptive growth and development rather than a pathological disturbance of normal progress.

The results of this study indicate the consideration of comprehensive, large-scale auxological surveys with the aim of elucidating the pattern, or patterns, of growth and development associated with CF. These studies should collect data on developmental, growth, and disease parameters and ideally should be of a mixed-longitudinal design. Only with such an approach can the implications of the maturational delays for growth in CF be fully assessed and the need for syndrome-specific standards be ascertained. Should these standards be implicated by such surveys, the data necessary to construct them will have already been acquired. Although the suggested scenario may appear logistically cumbersome, the potential benefits from such an approach would far outweigh the efforts involved in its conduct.

"Auxology is as essential a tool as radiology in the investigation of children's health and disease . . . [and] growth standards are the most powerful screening devices [in clinical auxology]" (Tanner, 1978c, p. 109). In order to obtain the full advantage of these powerful devices they must be relevant to the subjects being examined. The NCHS growth charts have been distributed

to the majority of pediatricians in the United States. Recommended for worldwide use by WHO and FAO, they are asserted to be applicable to "all United States children . . . [and] children in other countries . . . on the assumption that, with the exception of some small unusual groups, children of all countries would grow similarly . . . with the same environment" (Roche & Hamill, 1978, p. 138). In light of the results of the present study, perhaps those individuals with the most common hereditary chronic childhood disorder in Caucasians of western European descent are one of those small, unusual groups who do grow differently.

Clinical Auxology and Biological Anthropology: Implications for CF Research

The implications of the results of this research for the study of human biological variation stem from placing both human development and chronic disease within the same phylogenetic framework. Failure to refute the hypothesis of functional adaptation for developmental retardation in cystic fibrosis enhances our understanding of the possible relationships among human ontogenetic variation, disease, and phylogeny. The argument for the adaptive significance of this developmental variant would be made all the more tenable if it could be demonstrated to be associated with decreased mortality and/or increased

fertility. Specific research to test such associations should follow the re-implementation of the present protocol on a larger scale.

(1)(a) The suggested research should be directed toward the examination of the relationships among the same variables as in this study but in a larger sample; preferably involving 250-300 patients from several different regional CF centers. With this sample size, the format of the study could be changed from the present cross-sectional survey to a mixed-longitudinal one. This change in survey sampling would require a two-year data collection period at least but would return, with the proper sample size, more accurate data concerning developmental patterns and rates than the cross-sectional survey; especially for the sexual maturational indicators. In addition, a full battery of clinically relevant anthropometrics, such as stature, weight, diameters, circumferences, and skinfolds, would be recommended to test for growth delays concomitant with any maturational ones observed.

(1)(b) If possible, a coordinated project in which many of the same data are recorded for nonafflicted siblings and obligate heterozygote parents of the subjects is strongly recommended. Such data are extremely rare and may hold further information concerning familial genetic influence in both development and growth patterns.

Tanner and colleagues, for example, have advocated the application of centiles corrected for parental metrics (1978b) for similar evaluations in clinical studies.

A second line of inquiry suggested by the present study was touched upon briefly earlier. Whereas the re-implementation project might have been described as predominantly clinical in focus, the determination of the nature of the suggested functional adaptation in CF is more clearly of interest to biological anthropology. Two sets of observations, one from this study and the other from the literature, have prompted the following recommendations.

(2)(a) Recent studies have elucidated what the researchers interpret as evidence of phenotypic heterogeneity in syndrome composition in CF (Corey et al., 1980; Sing et al., 1982). Distinctive patterns of disease present with different combinations of pulmonary, pancreatic, and electrolyte abnormalities. Of special interest would be the examination of developmental patterns in individuals classified as exhibiting one disease phenotype as opposed to another. The observation of a different, but not significant, pattern of correlations for the males in this study, in comparison to those for the females, might be an indication of some degree of heterogeneity in the developmental pattern as well.

(2)(b) Additionally, an investigation of the association between the elucidated pattern(s) of CF development and mortality could provide insight into the nature of the functionally adaptive response postulated for CF. Such a project could be conducted only if at least one variant for the developmental pattern described in this study had been indicated to exist in frequencies high enough to preclude mutation as the explanation. If there is no variation in the developmental pattern for a sample, no relative survival values are obtainable.

Summary

The primary objective of this research was to test the general hypothesis that the pattern of delayed growth and development observed in cystic fibrosis patients is a functional adaptation to the stress imposed by the chronic hereditary disease itself. To test the general hypothesis, three alternative hypotheses were advanced. They were:

(1) If dental maturation was normal, but skeletal and sexual maturation were retarded and exhibited significant correlations with a disease severity score, then CF development would be considered a pathological response to disease stress;

(2) If dental maturation was normal, but skeletal and sexual maturation were retarded, displaying an insignificant correlation with disease severity and a significant correlation with age at diagnosis, then CF development could be considered an acclimatizational response to disease stress; and

(3) If dental, skeletal, and sexual maturation were found to be similarly retarded and exhibited an insignificant correlation with disease severity, then CF development would be considered a functional adaptation, predominantly under genetic influence.

Consistent patterns of retardation in dental, skeletal, and sexual maturation were observed. Significant correlations among the developmental indicators and between the developmental indicators and chronological age were observed. However, significant correlations between the developmental variables and disease severity were not observed. Consequently, the delays in the maturational indicators observed in this study are predominantly under genetic influence and are likely functional adapatations to the stress of cystic fibrosis. The role of natural selection cannot be demonstrated from these data and the functionally adaptive mechanisms still require confirmation by mortality studies, also not within

the scope of these data. However, the expression of a genetic effect on overall maturation is demonstrable.

Concluding Remarks

The study reported in this dissertation should be considered preliminary. It leaves in its wake as many new questions to consider as it answers concerning the role of development in cystic fibrosis in particular and the relationship between chronic hereditary disease and development in general. It is hoped that in some small way this research can contribute to our understanding of the proximate concerns of clinical auxology, especially in the case of cystic fibrosis, and to the ultimate relationships between human developmental and populational variation. It is not suggested herein that the application of evolutionary principles will provide all the auxological answers. It is, however, more likely that this approach has much to contribute by identifying the unasked questions which may have clinical, as well as phylogenetic, implications. Neither should this study be construed as a criticism of current research in cystic fibrosis. Rather, it is simply the result of looking at the same phenomena from another vantage point. There is no presumption that this work represents anything other than what it purports to be: an attempt to understand.

> False facts are highly injurious to the progress of science, for they often endure long; but false views,

> if supported by evidence, do little harm, for everyone takes a salutory pleasure in proving their falseness; and when this is done, one path towards error is closed and the road to truth is often at the same time opened (Darwin, 1871, in Maynard Smith, 1982, p. 6).

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