THIRD EDITION

Human Growth and Development









Edited by
Noël Cameron and Lawrence M. Schell

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Edited by

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In memory of James Mourilyan Tanner (1920—2010) and Francis E Johnston (1931—2020): teachers, mentors, colleagues, and friends.

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Special topics

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Acknowledgments

As the editors of the third edition of *Human Growth and Development*, we are acutely aware of the colleagues and students who have been instrumental in driving our enthusiasm to understand the biology of human growth and development. The complexity of the genetic, biochemical, physiological, and morphological processes that are evident during the process of human growth and are finally expressed in the variation of adult form that characterizes *Homo sapiens* create perhaps the most fascinating and awe-inspiring aspect of human biology. It has been our privilege to work with teachers, mentors, and colleagues over the last half century who have given freely of their time and expertise to further our understanding of the process of human growth. They have shared their knowledge through publications, lectures, conference presentations, seminars, and postmeeting discussions in bars and restaurants across the world. The pages of this volume pay homage to their combined influence for which we are very grateful.

Finally, it is the many thousands of students who we hope to have stimulated by our lectures, but who have in turn stimulated our desire to pass on knowledge, who are the true recipients of this work. Lecture theatres are places of intense activity, not only in the intrinsic interest of the information presented, but in the parry and thrust of the questions and answers that inevitably interrupt and follow each lecture. Students ask questions which often cause us to ponder the veracity of our information and view our evidence from different perspectives. It is they who are to be thanked for their excitement and enthusiasm with our sincere wish that they take the knowledge in this volume forward to add significantly to our understanding of the biology of human growth and development.

Noël Cameron and Larry Schell
March 2021

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Introduction

The second edition of *Human Growth and Development* is now almost 10 years old. Given the pace of discovery in the biological, medical, and social sciences relating to human growth a new edition is needed.

All chapters from the second edition have been updated and some have new authors, including younger emerging scientists who are destined to make important contributions to Human Biology and will be future standard bearers for the study of Auxology. The third edition also has a new coeditor, Professor Lawrence M Schell, who has been a colleague and critical friend for over 4 decades and whose opinion and insights have helped to guide the contents of this latest edition.

Using this book

The philosophy of how to use this book has not changed between editions. The chapters or lectures within this volume have been designed so that a "core" course can be extracted that provides information on the most important issues. For example, assuming that the first introductory chapter is always included, a class of human biologists or anthropologists would also need the lectures on infancy and childhood, juvenile growth, adolescence, puberty, and evolution to understand the basic biology. To these could be added the lectures on social, economic, and environmental issues and the methodological lectures to equip them with the skills for fieldwork. Preclinical and/or clinical students would need to understand the basic biology but also include lectures on genetic epidemiology, endocrinology, and assessment procedures in growth and maturity. According to need, other lectures on nutrition, biological modeling, the importance of early environments, physical activity, and body composition may be included. In this way, a series of lectures can be created to cater for the needs of a variety of audiences, e.g., medical, allied medical disciplines (physiotherapy, occupational therapy, nursing, etc.), dentistry, anthropology, human biology, education, sports science, sociology, psychology, and any other course dealing with children that will necessarily include information on human growth and development. Almost all lectures carry their own reference list or bibliography divided into three sections: (1) Suggested readings of the most useful items for students,

(2) Internet resources, often with high-quality illustrations, videos, and animations to enhance learning, and (3) References of the literature cited in the chapter.

Final year students, graduates, and those who have wandered in the vale of academe for many years will appreciate the old adage that "organizing academics is like herding cats." Their very independence of thought and action is what makes them the free thinkers that they are. Thus, to get them all to conform to a specific style is not even a remote possibility. This results in a series of lectures that vary in format. Some lecturers have chosen to lecture as they would present a scholarly textbook chapter, while others have been more expansive and less formal. In any case, we consider this variability to be a strength. The student will not be faced by a stereotyped series of lectures, just as in the university lecture theatre no two lecturers are the same.

Even so, the contributors were requested to design their chapter as a lecture that can be given in approximately 60 minutes. The limited time for each lecture is based on the duration of a normal university lecture of approximately 60 minutes and forces the lecturer to focus on the essential information. Most, but not all, lecturers have provided an Abstract or Introduction to open their chapter and a Summary and/or Conclusion. These may serve as memory aids of the most important information, once the entire chapter is read. Through the reference list, the lecturer may guide the students toward extending their knowledge.

The Lecturers

The first six lectures provide the core of a course on human growth in which the biological process of growth from birth to adulthood is described. As a senior editor, I have crafted the first chapter to form an introduction to the pattern and biology of human growth and development, the major areas that will be covered by the following 18 chapters. This broad overview is very much reflected by my breadth of experience and research in human growth and development. I completed my PhD supervised by James Tanner at the Institute of Child Health at London University whilst concurrently acting as the "clinical auxologist" for Tanner's growth disorder clinics at the Hospital for Sick Children, Great Ormond Street, London, in which I assessed the growth and skeletal maturation of each child attending the clinics. With this dual role, I was receiving probably the best available education and experience in the research techniques applied to both normal and abnormal growth. A personal statement later in this introduction provides more background to my education and interests.

There has been a change of personnel and some new lecturers have been invited to contribute. Dr Tom Norris, who provides a new lecture on prenatal and infant growth (Chapter 2), completed his PhD at Loughborough University under my supervision and

has made significant contributions to our understanding of fetal growth. He has an enviable attention to detail and a writing style that students will find accessible and enjoyable.

Dr Amanda Thompson graduated from Emory University under the supervision of Professor Michelle Lampl and completed her postdoctoral training at North Carolina where she was influenced by globally respected scientists within nutrition and international health such as Professors Penny Gordon-Larsen and Linda Adair. Amanda brings a broad and detailed approach to the developing child and has made an excellent contribution to this volume.

Professor Bradley Miller, from the University of Minnesota at Minneapolis, brings a wealth of clinical knowledge and experience to provide details not only of the complex nature of the endocrine control of human growth and maturation but also of growth disorders in Chapter 6. The chapter is detailed but entirely accessible as it links the biology of the endocrine system with the complexities of its control of growth with great lucidity.

Professor Slawomir Koziel from the Hirszfeld Institute of Immunology and Experimental Therapy in Poland undertakes research concerning among other things the biological and health consequences of social phenomenon, the effects of prenatal and early childhood stress on growth and development, studies on the biological aspects of horizontal and vertical social mobility, and on biological consequences of economic and political transition. He is well qualified to discuss the effect of social and economic factors on human growth.

Dr Emily Rousham has linked up with my coeditor Lawrence Schell to provide an exhaustive chapter on the environmental factor affecting growth (Chapter 10). She is a Cambridge graduate at both undergraduate and postgraduate levels working under the supervision of Professor Nicholas Mascie-Taylor for her PhD studies on the effect of antihelminthic treatment on child growth and nutrition in Bangladesh. Emily's research covers community-based studies of maternal and child health and the relationship between nutrition, growth, and infection in children in low resource settings. Her current research projects lie at the intersection of communicable and noncommunicable diseases, and the social, environmental, and behavioral factors that contribute to global health challenges.

Dr William Johnson is another of my own ex-PhD students from Loughborough University. His background is therefore in Human Biology with significant postdoctoral work with Professor Ellen Demerath at the University of Minnesota's Division for Epidemiology and Community Health, the UK Medical Research Council's Unit for Lifelong Health and Ageing at University College London, and MRC Human Nutrition Research. Will Johnson works with birth cohort and other longitudinal studies on a

program of research investigating the etiologic factors regulating human growth and development; the consequences of body size and composition trajectories for health and wellbeing; population-level variation (e.g., temporal) and individual-level heterogeneity in the development, causes, and consequences of obesity; and statistical methods to model longitudinal data and investigate complex associations, particularly multilevel growth curve modeling. He is one of the leading researchers using advanced statistical methods to model human growth and has developed an international reputation for his work.

Professors Debi Bolter and Adrienne Zihlman, from Modesto College and the University of Santa Cruz, respectively, are the leading researchers into the evolution of patterns of human growth through their renowned research on the growth of nonhuman primates. The principles implicit in the study of the growth of apes and humans have been applied to the evidence for ontogeny in our hominin ancestors. I have been privileged to work with Dr Bolter on the most recent hominins, *Homo naledi*, from the Rising Star cave system in South Africa and am delighted that she brings her expertise to this volume.

Professor Sean Cummings and Lauren Sherar, of the Universities of Bath and Loughborough, respectively, are the foremost researchers in the relationship between physical activity and growth. Professor Sherar's research area is in the associations among physical activity/sedentary behavior, body composition, and cardiometabolic health in children and adolescents. She has a specific interest in the investigation of biological, social, and environmental determinants of activity and sedentary behaviors in a manner to inform interventions. Dr Sean Cumming is internationally recognized as a leading expert on the subject of growth and maturation in sport and exercise. Adopting a biocultural perspective, his research seeks to understand how biological and psychosocial factors impact athletic development and the maintenance of health behaviors during adolescence. Together they form a formidable team to discuss the relationship between physical activity and human growth.

Professor Audrey Chou of the University of Texas School of Public Health teams up with Professor Stefan Czerwinski. Both are ex-PhD students of Professor Lawrence Schell from the State University of New York at Albany. Internationally known for their work on the genetics of growth, body composition, and cardiovascular disease, they have updated Chapter 8 on genetics, epidemiology, and growth.

The other lecturers in this volume will be familiar from the first two editions of this volume. They have graciously continued to give freely of their time and expertise in updating their previous contributions thereby maintaining the currency of this edition.

Editors' Personal Statements

Noël Cameron

This book has its origins in my own series of lectures on human growth and development given to undergraduates attending British and South African universities over the last 45 years. In 1976, while studying for my Doctoral degree under the supervision of Professor James Tanner at London University's Institute of Child Health, I was asked to give an annual series of lectures to Biological Anthropology students at Cambridge University. At about the same time, the geneticist Professor Alan Bittles, at Chelsea College, London University, asked me to provide a similar series of lectures to his students.

In the 1970s, there were not many textbooks that one could use as coursework references for students of biology and anthropology. There were a number of texts, almost exclusively from America, describing the growth and development of children. Ernest Watson and George Lowery, Pediatricians at the University of Michigan Medical School, had first published the *Growth and Development of Children* in 1951.[1] The Physical Anthropologist and Human Biologist, Stanley Garn, then Chairman of the "Physical Growth Department" at the Fels Research Institute in Ohio, collaborated with the Israeli pediatrician Zvi Shamir from Jerusalem to publish *Methods for Research in Human Growth* in 1958.[2] Donald Cheek of Johns Hopkins University published *Human Growth: body composition, cell growth, energy and intelligence* in 1968[3] and Wilton Krogman, from the University of Pennsylvania, had published his very useful *Child Growth* in 1972.[4] In 1966, a landmark work edited by Frank Falkner was destined to be the forerunner to several more recent texts in similar style. It was simply called *Human Development* and was, I think, the first volume to use different "authorities" (29 in this case) to provide the breadth and depth required to understand this most diverse of subjects.[5] However, with some notable exceptions, almost all these volumes had been written by pediatricians interested in the clinical aspects of the subject rather than the biology of growth. In addition to the usual descriptions of the pattern of human growth, they were replete with diagnostic criteria and assessment procedures. They had little in the way of discussion about broader topics and the biological and conceptual basis of growth and development. In the United Kingdom, Tanner's *Growth at Adolescence*, first published in 1959,[6] was the classic core text to be supplemented by a variety of scholarly scientific reviews and research papers to cover preadolescent growth and some other areas in greater depth. Later, his *Fetus into Man* (1978) partially made up for this deficit, but it was to some extent an introductory text and there was still the need for greater depth to be added through specific references.[7] In the same year (1978), Frank Falkner joined forces with his friend (and previous colleague) Jim Tanner to edit the three-volume series *Human Growth: a comprehensive treatise* that was an excellent library resource but was far too expensive

and detailed for the undergraduate or graduate student.[8] Clearly, by the 1970s, many of the earlier texts were becoming dated.

During my sojourn in South Africa, between 1984 and 1997, I lectured to large classes of students studying medicine and the allied medical disciplines (dentistry, physiotherapy, occupational therapy, and nursing) in addition to smaller classes of medical science students. Within the large formal lecture classes of 400 or more students, there was a relatively restricted opportunity for discussion but the clear need to portray the biology of human growth in an immediate and vivid way in a short series of five or six lectures. The smaller medical science classes allowed me the freedom to "discuss" rather than "teach" human growth and development and to do so in an expansive series of 15 lectures covering half the academic year. By this time, I was invariably recommending Tanner's *Growth at Adolescence* and *Fetus into Man* in addition to specific contributions from Falkner and Tanner's "comprehensive treatise." The first edition of Barry Bogin's "*Patterns of Human Growth*" became an accepted alternative text for this audience on its publication in 1988.[9] However, like *Fetus into Man*, it suffered from being written from the perspective and knowledge of a single author and thus lacked the breadth, and at times the depth, to be universally recommended.

Out of these experiences came the awareness that if I were to require a single reference text that catered for students of all disciplines, then I would have to create it myself. Central to these thoughts was the knowledge that no single scientist could hope to properly cover the different aspects of human growth and development with the breadth and depth required. Rather what was needed was a team of lecturers and, if the text was to be the best possible text, this team would have to be recognized international experts in their fields of interest. They would indeed be a "dream team" that would, in effect, be invited into the lecture theatre to provide a one-hour discourse on their subject. The target audience was the senior undergraduate student and/or immediate postgraduate student, i.e. the American "graduate student." The text would not only cover the important issues in human growth and development, but would also allow the contributors the freedom to add greater breadth and depth through a good annotated reference list and a variety of recommended web sites.

Thus was this particular volume conceived

I am delighted that my colleague and friend, Professor Lawrence Schell, accepted my invitation to become my coeditor for this third edition of *Human Growth and Development*. Larry Schell has had a distinguished academic career in anthropology and public health. His interest in human growth and particularly in the effects of environmental stressors began almost 40 years ago while he studied for his PhD under the supervision of Francis E Johnston at the University of Pennsylvania. Now he is recognized

as the leading authority on the effect of environmental pollutants on human growth. His long teaching experience at the State University of New York at Albany, his attention to detail, and his steady hand directing my enthusiasm and energy have undoubtedly added significantly to this work.

As editors, we have had the mostly pleasurable experience of seeking some degree of rationality. Of attempting to create an ordered series of lectures that will be of major benefit to students and lecturers alike. We thank all of the contributors for their willingness to cooperate in this venture and appreciate that most have been under considerable pressure but have nevertheless been timeous and gracious in their dealings with us. We thank my friends and colleagues within the science of auxology who have encouraged us to complete this task and hope that their confidence in our ability to produce a worthwhile volume has not been misplaced.

Lawrence Schell

I am very pleased that Professor Noel Cameron has asked me to assist with the third edition of *Human Growth and Development*. I have been using the text through both the first and second editions in many years teaching my advanced course in growth and development. As the field has advanced, so too will the text, and I am glad to be able to help with refashioning the third edition.

Growth and development was not my starting point in human biology. While in secondary school, I became interested in the evolution of the species and I took my first anthropology class then. Much later, I met Albert Damon of Harvard University who introduced me to the subject of human biology, how our evolution and biological change had not stopped with the advent of modern life and culture, but was continuing under new influences. I wanted to know what those were. I began studying with Frank Johnston at Temple University, and when he moved to the University of Pennsylvania, I moved with him. As an undergraduate major in anthropology, I had not been interested in growth, but through Frank's teaching and writing, I came to see it as a means of adaptation and a slate on which the human-made environment makes an indelible mark.

The most obvious challenge in modern life, the sharpest difference from the environment of our evolutionary past, is urban living. Among the many changes in human experience was the increase in stress caused by city living. I wanted to know if urban stress was sufficiently powerful to affect child growth. In that period, the tools for measuring stress in populations were primitive and expensive by today's standards. Thus, to study the effect of stress on the growth, I used an environmental surrogate, aircraft noise, which reliably produces a stress reaction. As it turned out, the major effects of noise were on the fetus as indexed by newborn size and so I began my interest in prenatal experience as an influence on later growth and health. I continued to research the effects of the human-made

environment on human biology by expanding my focus to include other factors that were newly created such as industrial chemicals and pesticides (e.g., DDT) and old familiar exposures experienced but which were now experienced at very high levels such as metals (lead, mercury).

Now for the third edition, I see more attention paid to prenatal growth, the impact of social as well as physical environmental influences, and their long-term consequences. Growth, as a field of study, is more relevant now than ever before. Providing a thorough treatment of the most important topics is an important contribution.

Coda

The editors hope that students will find within these pages a biological story that will excite and fascinate them as it has done to us for the last 4 decades. The process of growth and maturation is one that every living thing in the history of our planet has experienced. We do not think that the complexity of that process has reached or will reach an end point with *Homo sapiens* because the process of human growth is constantly dynamic and constantly changing in response to the changes in the environment, both global and local, in which we live. Indeed, it is this plasticity, resulting in the wonderfully varied species which we see around us, that makes the process of human growth so fascinating.

Noël Cameron
Lawrence Schell
March 2021

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CHAPTER 1

The pattern of human growth

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Introduction

Human growth and development are characterized and defined by the way in which we change in size, shape, and maturity relative to the passage of time. It has been more common for the size of children to be assessed for reasons of classification and organization that requires assessment at certain ages for specific reasons. However, the first longitudinal record we have of the growth of a child *was* the result of a desire to apply scientific method to the natural world.

Historical background

The pursuit of natural science, and in particular the elucidation of the pattern of human growth, has its origins in the "Age of Enlightenment" in 18th century France. Between the death of Louis XIV in 1715, and the coup d'état of the November 9, 1799 that brought Napoleon Bonaparte to power, philosophy, science and art were dominated by "The Enlightenment"; a movement away from religious and monarchical authority and dogma and toward a more liberal and empirical attitude.[1] The natural scientists and philosophers of the Enlightenment believed that people's habits of thought were based on irrationality, polluted by religious dogma, superstition, and over-adherence to historical precedent and irrelevant tradition. The way to escape from this, to move forward, was to seek for true knowledge in every sphere of life, to establish the truth and build on it. People's minds were, literally, to be "enlightened".[2] Its primary impulse was in pre-Revolutionary France within a group of mostly aristocratic and bourgeois natural scientists and philosophers that included Rousseau, Voltaire, Diderot and Georges Louis LeClerc, the Compte de Buffon (Fig. 1.1). Their contributions to Diderot's Encyclopedia – the first literary monument to the Enlightenment – earned them the collective title of "the Encyclopedists".

Georges Louis LeClerc was born on September 7, 1707 at Montbard in Bourgogne, Central France. His father, Benjamin-Francois LeClerc, described by the biographer

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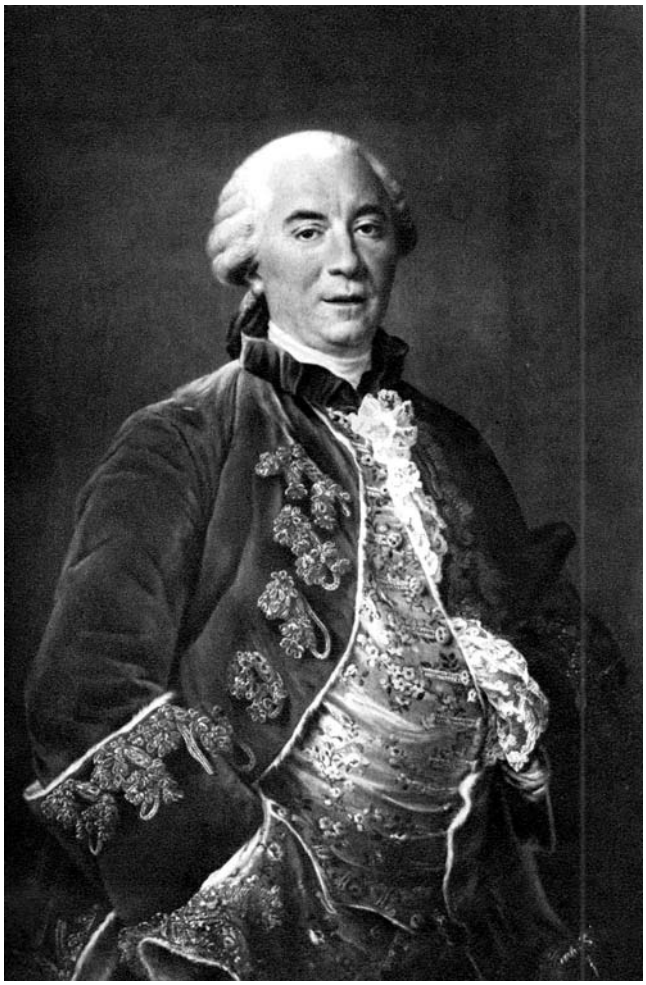

Fig. 1.1
Georges-Louis LeClerc, Compte de Buffon (1707–88).

Franck Bourdier as "un homme sans grand charactère," was a minor parliamentary official in Burgundy and was married to an older woman, Anne-Christine Marlin[3]. In 1717 Anne-Christine inherited a considerable fortune from an extremely wealthy uncle, Georges Blaisot, which allowed Monsieur LeClerc to buy the land of Buffon and the "châtellenie" of Montbard in Burgundy. Georges Louis was educated by the Jesuits at the Colleges de Godran where he demonstrated an aptitude for mathematics. In 1728, at the age of 21, he moved to the University of Angers and thence suddenly to England following a duel with an officer of the Royal-Croates over "une intrigue d'amour." He traveled in Switzerland, France and Italy during the next four years returning to Dijon on the death of his mother in 1732. Much against his father's wishes he inherited his mother's estate at Montbard and

subsequently divided his time between Paris and the country pursuing his interests in mathematics, natural science, and silviculture, the cultivation of trees. By the age of 32 he was recognized as the premier horticulturist and arborist in France and was appointed by King Louize XVth as the director of the Jardin du Roi in 1739. The Jardin du Roi was originally the Royal Garden of Medicinal Plants and was to eventually become the National Museum of Natural History to include galleries (museums) of zoology, minerology, geology, palaeontology, comparative anatomy, botany, and, most recently, evolution. The position of Director was the most prestigious governmental scientific position in the "natural sciences" and wielded enormous influence. Having been invited by the king to write a compendium on the herbs of France, Buffon decided that such a compendium would be too narrow and instead Buffon started to work on a far broader project that was to include *all* that was known of natural history. *"Histoire Naturelle, Générale et Particulière"* would be a vast undertaking but one that Buffon, who from all accounts was a man of no small ego, appeared to relish and which by his death in 1788 was composed of 36 volumes. There were 15 volumes on quadrupeds (1749–67), nine on birds (1770–83), five on minerals (1783–88), and seven "Supplementary Volumes." Eight further volumes were added posthumously between 1788 and 1804 authored by Bernard Germain de Lacépède who had been appointed as a sub-demonstrator in the Jardin in 1785. Lacépède was to become one of France's leading natural scientists elected as "perpetual secretary" of the French Academy of Sciences at the Institute of France in 1796, a Fellow of the Royal Society in 1806, a foreign member of the Royal Swedish Academy of Sciences in 1812, and eventually a politician and statesman. The eight volumes included two on reptiles (1788–89), five on fish (1798–1803), and one on *Cetacea* (1804). However, it is the supplement to volume 14, published in 1778, that is particularly interesting to us.[4]

Within this supplement on page 77 there is the record of the growth of a boy, François Guéneau De Montbeillard (1759–1847). His father, Philibert Guéneau De Montbeillard (1720–85) was a close friend of Buffon and their common interest in the natural sciences resulted in De Montbeillard being invited as a co-author in 1770. Buffon had been working closely for many years with his younger neighbor from Montard, Louis-Jean-Marie Daubenton (1716–99), whose statue now adorns the Parc Buffon in Montard (while Buffon's statue is to be found in the Jardin des Plantes in Paris). Daubenton had graduated in Medicine in Reims 1741 and returned to Montard to set up practice as a physician. This coincided with Buffon's initial preparations for the first volumes of Histoire Naturelle and in 1742 he invited Daubenton to provide a series of anatomical descriptions of animals. Daubenton's subsequent descriptions of 182 species of quadruped that appeared in the early volumes of Histoire Naturelle established him as the foremost comparative anatomist of his day. However, De Montbeillard was to replace Daubenton in Buffon's affections and between 1770 and 1783 De Montbeillard co-authored the nine volumes of Histoire

Naturelle devoted to birds. He was also a correspondent of Diderot and clearly recognized as one of the Encyclopedists. Given the desire of these central scientific figures of the Enlightenment to measure and describe the natural world it is neither too surprising that De Montbeillard would take an empirical interest in the growth of his own son, François, nor is it inconceivable that his friend and colleague Buffon would wish to include this primary evidence of the course of human growth within his *magnum opus*.

De Montbeillard had been measuring the height of François about every 6 months from his birth in 1759 until he was 18 years of age in 1777. François was clearly no stranger to the scientific pursuits of his father having been inoculated by him in 1766 against smallpox, which was a controversial procedure at the time. The measurements of height were reported in the French units of the time; pieds, pouces, and lignes which correspond roughly to present day units as a foot, inch and the 12th part of an inch. A pieds was in fact a variable length depending on where one lived in France. While, in modern Système Internationale (SI) units, the pieds du Roi was 324.8 mm, the pieds d'Angoulême was 347.0 mm, in urban Bordeaux it was 343.6 mm and in rural Bordeaux 357.2 mm, but in Strasbourg it was 295.0 mm.[5] So, it was clearly financially advantageous to buy commodities measured by length in rural Bordeaux and sell the same in Strasbourg to make about a 20% profit as result of differences in the length of a foot! The importance of this lack of standardization both nationally and internationally was of primary concern to the Académie de France and in the 1790s they set up a project to standardize measurement based on the natural world. They did so by using one ten millionth of the distance from the North Pole to the Equator on a line passing through Dunkerque, Paris and Barcelona as a length of one meter. The account of this quest for standardization is one of the great stories of the emergence of modern scientific method and is told remarkably well by Adler.[1]

Richard E. Scammon (1883–1952) of the Department of Anatomy and the Institute of Child Welfare at the University of Minnesota, translated the measurements of De Montbeillard into SI units. He published his results in 1930 in the American Journal of Physical Anthropology under the title of "The first seriatim study of human growth" and thus for the first time we were able to look upon the pattern of growth exhibited by François Guéneau De Montbeillard in the form of a chart.[6]

The distance curve of growth

By joining the data points at each age, Scammon produced the "height-for-age" curve that also became known as a "height distance" curve (Fig. 1.2). We use the term "distance" to describe height achieved because it is easy to visualize and understand the fact that a child's height at any age is a reflection of how far that child has progressed toward adulthood. It embodies the sense of an ongoing journey that we are, as it were,

Fig. 1.2
The growth of François De Montbeillard 1759–77: distance. *Redrawn from Tanner JM.* Growth at Adolescence. *2nd ed. Oxford: Blackwell Scientific Publications; 1962.*

interrupting to take a "snapshot" at a particular moment in time. The resulting curve is interesting for a number of reasons. Firstly, when growth is measured at intervals of 6 months or a year, the resultant curve is relatively smooth depicting a continuous process. Secondly, growth is not a *linear* process; we do not gain the same amount of height during each calendar year. Thirdly, the curve of growth has five distinct phases corresponding to (1) relatively rapid growth in infancy, (2) steady growth in childhood, (3) a short period of rapid growth during the juvenile period, (4) a second period of rapid growth during adolescence, and (5) very slow growth as the individual approaches adulthood. Fourthly, growth represents a most dramatic increase in size; François De Montbeillard, for instance, grew from about 50 cm at birth to over 186 cm at adulthood. The majority of that growth (more than 80%) occurs during infancy and childhood but perhaps the most important physical changes occur during adolescence. Fifthly, we cease growing, reaching our adult height, during our late teenage years.

The pattern of growth that we can see from this curve is a function of the frequency of data acquisition. If we were to only measure a child at birth and at 18 years we might believe, by joining up these two data points, that growth was a linear process. Clearly the

more frequently we collect data the more we can understand about the pattern of growth on a yearly, monthly, weekly, or even daily basis. Such high frequency studies are logistically very difficult and thus there are only a very few in existence. Perhaps the most important are those of Dr. Michelle Lampl who was able to assess growth in length, weight, and head circumference on a sample of 31 children on daily, bi-weekly and weekly measurement frequencies.[7] The resulting data demonstrated that growth in height may not be a continuous phenomenon but may actually occur in short bursts of activity (saltation) that punctuate periods of no growth (stasis) (see Chapter 18). However, the data we have for François De Montbeillard was collected approximately 6-montly and thus at best it can only tell us about the pattern of growth based on a half-yearly or yearly measurement frequency.

It is clear that the pattern of growth that results from these 6-monthly measurements is in fact composed of several different curves. During infancy and early childhood, between birth and about 5 years of age, there is a smooth curve that gradually departs negatively from a straight line as time increases. In mathematical modeling terms this is described as a "decaying polynomial" curve. During childhood, between 5 and about 10 years if age, the pattern does not depart dramatically from a straight line. The pattern changes during adolescence, between about 10 and 18 years of age, into an S-shaped or "sigmoid" curve reaching an asymptote at about 19 years of age.

The fact that the total distance curve may be represented by several mathematical functions (e.g. polynomial, logistic, and sigmoid functions) allows us to apply mathematical "models" to the pattern of growth. These models are, in fact, parametric functions that contain constants or "parameters." Once we have found an appropriate function that fits the raw data, we can analyze the parameters and by so doing learn a good deal about the biological process responsible for growth (see Chapters 4 and 13). For instance, in the simplest case of two variables such as age (X) and height (Y) being linearly related between say, 5 and 10 years of age, (i.e. a constant unit increase in age is related to a constant unit increase in height) the mathematical function $Y = a + bX$ (sometomes written as $Y = mX + c$) describes their relationship. The parameter "a" represents the point at which the straight line passes through the Y-axis and is called the intercept, and "b" represents the amount that Y increases for each unit increase in X, and is called the regression coefficient. The fitting of this function to data from different children and subsequent analysis of the parameters can tell us about the magnitude of the differences between the children and lead to further investigations of the causes of the differences. Such "time series analysis" is extremely useful within research on human growth because it allows us to reduce large amounts of data to only a few parameters. In the case of François De Montbeillard there are 37 height measurements at 37 different ages. Thus there are 74 data items for analysis. The fitting of an appropriate parametric function reduces the 74 pieces of information down to the number of parameters in the

function. In the widely used Preece-Baines function[8] that we will discuss later (see Chapter 4), this process reduces these 74 items to just 5 parameters. Because of their ability to reduce data from many to only a few items such parametric solutions are said to be parsimonious, in that they accomplish a desired level of explanation or prediction with as few predictor variables as possible. Consequently, they are widely used in research into human growth.

The velocity growth curve and growth spurts

The pattern created by changing rates of growth is more clearly seen by visualizing the rate of change of size with time i.e. "growth velocity" or, in this particular case, "height velocity." The term "height velocity" was coined by James Tanner[9] based on the writings of Sir D'Arcy Wentworth Thompson (1860−1948). D'Arcy Thompson was a famous British natural scientist and mathematical biologist who published a landmark biology text entitled "On Growth and Form" in 1917 with a second edition in 1942.[10,11] Thompson's core thesis was that structuralism, underpinned by the laws of physics and mechanics, was primarily responsible for variation in size and shape within phylogeny (i.e. within the evolutionary development of our species (see Chapter 15)). Considering allometry, the impact on the whole organism of varying growth rates of different body parts, D'Arcy Thompson wrote that, "An organism is so complex a thing, and growth so complex a phenomenon, that for growth to be so uniform and constant in all the parts as to keep the whole shape unchanged would indeed be an unlikely and an unusual circumstance. Rates vary, proportions change, and the whole configuration alters accordingly." Within the second edition (p. 95) Thompson wrote that while the distance curve, "showed a continuous succession of varying *magnitudes*," the curve of the rate of change of height with time, "shows a succession of varying *velocities*. The mathematicians call it a *curve of first differences*; we may call it a curve of the rate (or rates) of growth, or more simply a *velocity curve*." The velocity of growth experienced by François De Montbeillard is displayed in Fig. 1.3. The Y-axis records height gain in cm yr^{-1}, and the X-axis chronological age in years. We can see that following birth two relatively distinct increases in growth rate occur at 6−8 years and again at 11−18 years. The first of these "growth spurts" is called the juvenile or mid-growth spurt (see Chapters 2 and 3) and the second is called the adolescent growth spurt (see Chapter 4).

There is, in fact, another growth spurt that we cannot see because it occurs prior to birth (Chapter 2). Between 20 and 30 weeks of gestation the rate at which the length of the fetus increases reaches a peak at approximately 120 cm yr^{-1} but all we can observe after birth is the slope of decreasing velocity lasting until about 4 years of age. Similarly, increase in weight also experiences a pre-natal spurt but a little later, at 30−40 weeks of gestation. Of course, information on the growth of the fetus is difficult to obtain and relies

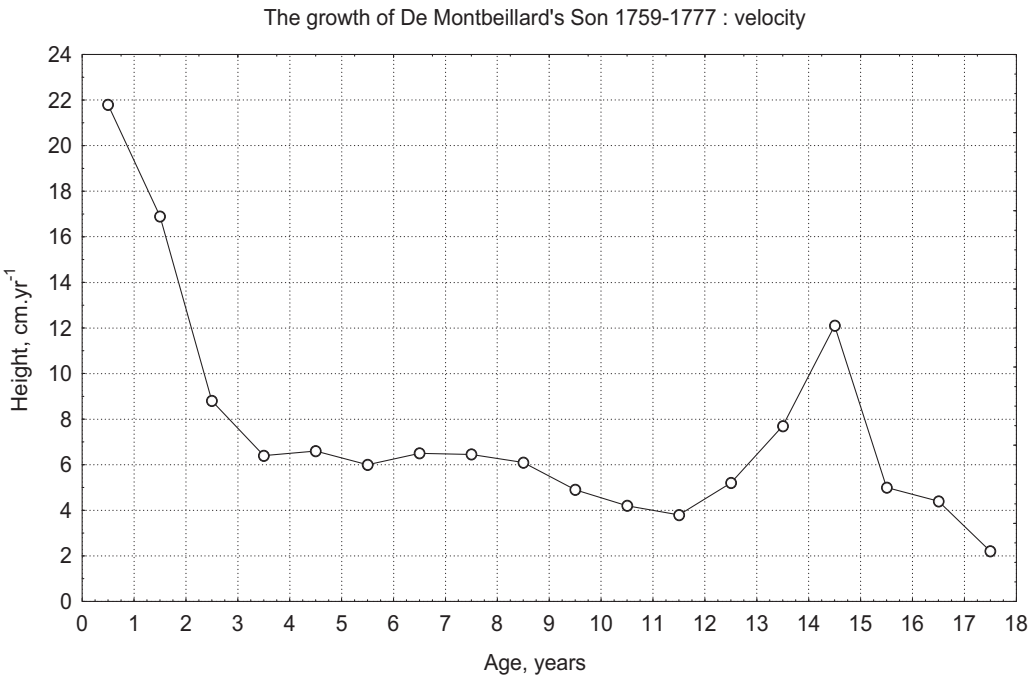

Fig. 1.3
The growth of François De Montbeillard 1759–77: velocity. *Redrawn from Tanner JM.* Growth at Adolescence. *2nd ed. Oxford: Blackwell Scientific Publications; 1962.*

largely on two sources of information: intra-uterine ultrasound measurements of fetuses and extra-uterine anthropometric measurements of pre-term infants. Ultrasound assessments of crown-rump length indicate that growth is smooth and rapid during the first half of pregnancy. Indeed it is so smooth between 11 and 14 post-menstrual weeks, when the growth velocity is 10–12 mm week^{-1}, that gestational age can be calculated from a single measurement to within $\pm$ 4.7 days. The 95% error band when three consecutive measurements are taken is $\pm$ 2.7 days. Intra-uterine growth charts for weight demonstrate that growth over the last trimester of pregnancy follows a sigmoid pattern and thus, like the sigmoid pattern reflected in height-for-age during adolescence, will also demonstrate a growth spurt when velocity is derived. The spurt should reach a peak at about 34–36 weeks. Why should the fetus be growing so quickly in terms of weight at this time? Results from an analysis of 36 fetuses in the mid-1970s demonstrated that between 30 and 40 post-menstrual weeks fat increases from an average of 30 g–430 g. This dramatic accumulation of fat is directly related to the fact that fat is a better source of energy per unit volume releasing twice as much energy per gram as either protein or carbohydrate. Thus a significant store of energy is available to the fetus for the immediate post-natal period. It is now recognized that the growth of fat in each place in which it is

deposited (fat depots) varies according to the mother's diet and if her nutrition is not optimum it can lead to risk of disease in later life through insulin resistance and glucose intolerance.[12] (see Chapter 16).

While the pre-natal spurt and juvenile growth spurt may vary in magnitude, they seem to occur at similar ages both within and between the sexes. The adolescent growth spurt, however, demonstrates sexual dimorphism in both magnitude and timing; males enter their adolescent growth spurt almost two years later than females and have a slightly greater magnitude of height gain. The result is increased adult height for males mainly resulting from their two years of extra growth prior to adolescence. At the same time other skeletal changes are occurring that result in wider shoulders in males and, in relative terms, wider hips in females. Males demonstrate rapid increases in muscle mass and females accumulate greater amounts of fat. Their fat is distributed in a "gynoid" pattern, in the gluteo-femoral region, rather than in the "android" pattern with a more centralized abdominal distribution characteristic of males (see Chapter 19). Physiologically males develop greater strength and lung capacity. Thus, by the end of adolescence a degree of morphological difference exists between the sexes; males are larger and stronger and more capable of hard physical work. Such "sexual dimorphism" is found to a greater or lesser extent in all primates and serves to remind us that these physical devices had, and perhaps still have, important sexual signaling roles.

The pre-adolescent period of childhood is peculiar to hominids (Homo erectus to *Homo sapiens*) and its existence raises important questions about the evolution of the *pattern* of human growth. Bogin[13] argues that humans have a childhood because it creates a reproductive advantage over other species through the mechanism of reduced birth spacing and greater lifetime fertility. In addition, slow growth during childhood allows for "developmental plasticity" in sympathetic response to a changing environment with the result that a greater percentage of hominid young survive compared to any other mammalian species.

Other patterns of growth

The pattern of growth in height, as demonstrated by François De Montbeillard, is only one of several patterns of growth that are found within the body. Fig. 1.4 illustrates the major differences in pattern as exemplified by neural tissue (brain and head), lymphoid tissue (thymus, lymph nodes, intestinal lymph masses), and reproductive tissue (testes, ovaries, epididymis, prostate, seminal vesicles, Fallopian tubes) in addition to the general growth curve of weight and some major organ systems (respiratory, digestive, urinary). Growth in height demonstrates a somewhat different pattern, not represented by the "general" curve, with about 80% of adult size being achieved by about 12 years of age. While the data on which this Figure is based were originally published by R.E. Scammon in 1930,[14] they are

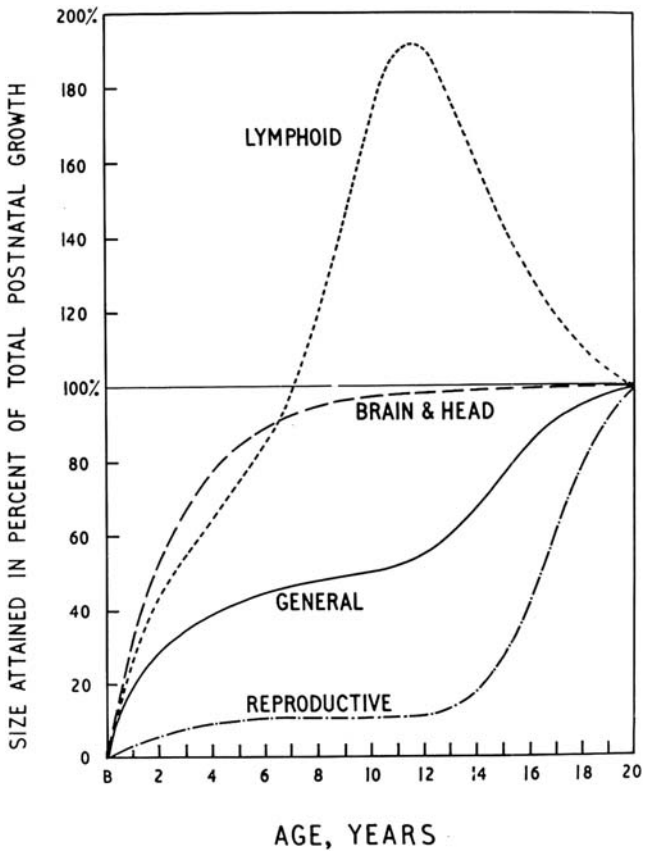

Fig. 1.4

Growth curves of different parts and tissues of the body, showing the four main types: *lymphoid* (thymus, lymph nodes, intestinal lymph masses); *brain, neural tissue and head* (brain and its parts, dura, spinal cord, optic system, cranial dimensions); *general tissue* (whole body weight, respiratory and digestive organs, kidneys, aortic and pulmonary trunks, musculature, blood volume); *reproductive tissue* (testes, overy, epididymis, prostate, seminal vesicles, fallopian tubes. *From Tanner JM.* Growth at Adolescence. *Blackwell Scientific Publications; 1955.*

sufficient to allow us to appreciate that lymphoid, neural, and reproductive tissue have very different patterns of growth to the general growth curve we initially observed. Neural tissue exhibits strong early growth and is almost complete by 8 years of age while reproductive tissue does not really start to increase in size until 13 or 14 years of age. The lymphatic system, that acts as a circulatory system for tissue fluid and includes the thymus, tonsils and spleen in addition to the lymph nodes, demonstrates a remarkable increase in size until the early adolescent years and then declines perhaps as a result of the activities of sex hormones during puberty (see Chapters 5 and 6). The majority of our interest in this and other lectures on growth concerns the pattern of growth as exhibited by

height and weight. It is clear, however, that research on the growth of neural tissue must be targeted at fetal and infant ages and research on the growth of reproductive tissue on adolescent or teenage years when growth is at a maximum.

Growth versus maturity

While we have illustrated growth thus far by using the pattern demonstrated by one boy in 18th Century France, it is now evident that his curves of growth (i.e. distance and velocity) reflect patterns that are found in *all* children who live in normal environmental circumstances. We may differ in the magnitude of growth that occurs, as is evident from our varying adult statures, but in order to reach our final heights we have all experienced a similar pattern of growth. It is clear that the pattern of growth in height is not the only form of somatic growth that occurs in the human body. We have already discussed the fact that as we experience the process of growth in linear dimensions i.e. as we get taller, we also experience other forms of growth; we get heavier, fatter, and more muscular and we experience changes in our body proportions. In addition, we become more "mature" in that we experience an increase in our functional capacity with advancing age that may be evidenced in our increasing ability to undertake physical exercise in terms of both magnitude and duration (see Chapter 17). Although we tend to think of "growth and development" as a single biological phenomenon both aspects have distinct and important differences. "Growth" is defined as an increase in size while "maturity" or "development" is an increase in functional ability. The end-point of growth is the size we attain by adulthood, roughly corresponding to growth rates of less than 1 cm yr^{-1}, and the end-point of maturity is when we are functionally able to successfully procreate. That is not simply to be able to produce viable sperm in the case of males and viable ova in the case of females. Successful procreation in a biological sense requires that the offspring survive so that they themselves may also procreate. Thus, successful maturation requires not just biological maturity but also psycho-social and behavioral maturity.

The relationship between somatic growth and maturity is perhaps best illustrated by Fig. 1.5. The figure shows three boys and three girls who are of the same ages within sex; the boys are exactly 14.75 years of age and the girls 12.75 years of age. The most striking feature of this illustration is that even though they are the same age they demonstrate vastly different degrees of maturity. The boy and girl on the left are relatively immature compared to those on the right as depicted by their indicators of maturity or "maturity indicators" (see Chapter 12). These may well include the obvious development of secondary sexual characteristics (breast and pubic hair in girls and genitalia and pubic hair in boys), in addition to dramatic changes in body shape, increases in muscularity in males and increases in body fat in females. If we look carefully we can see that distinct changes in the shape of the face also occur, particularly in boys, that result in more robust features

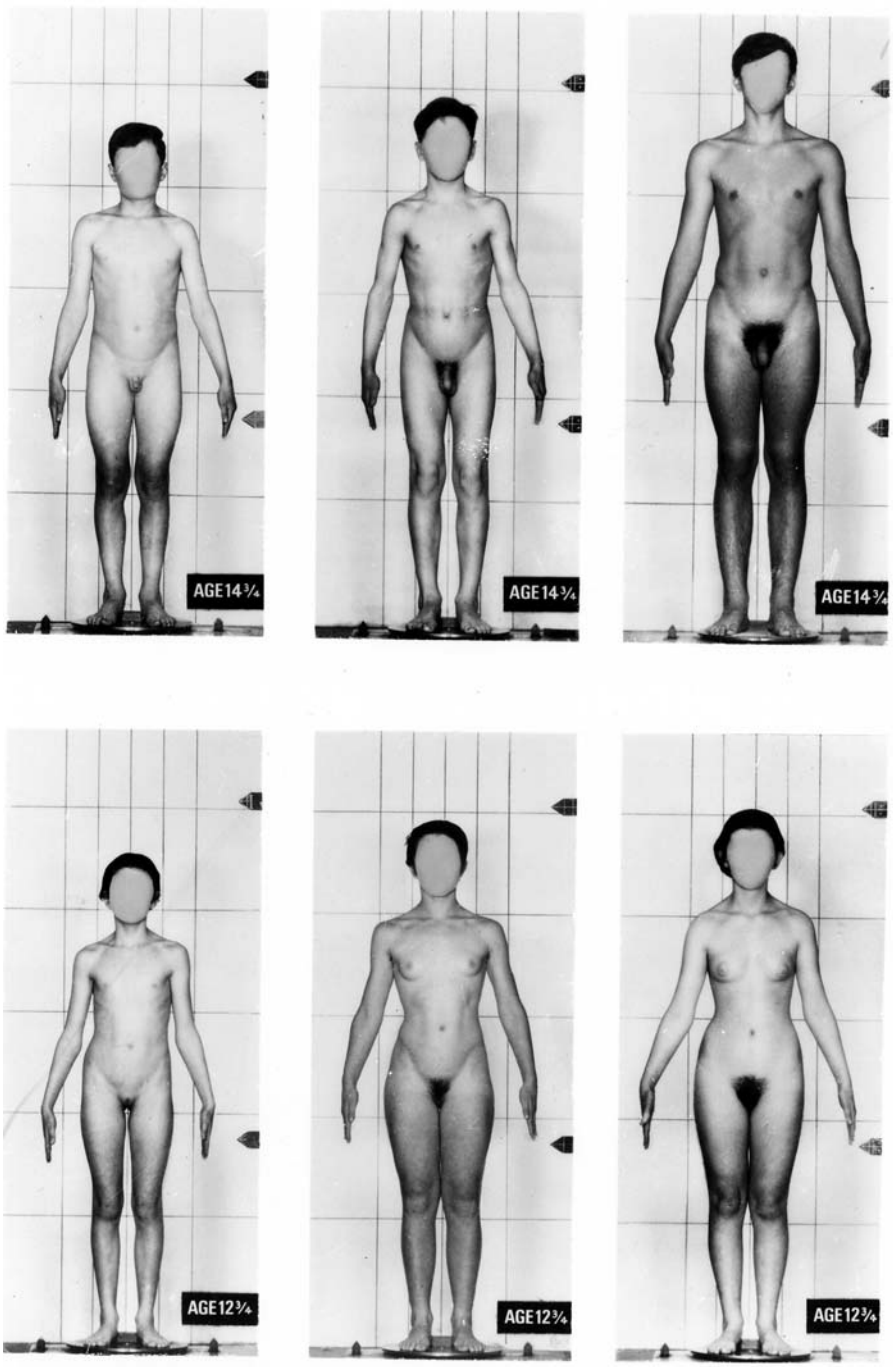

Fig. 1.5

Three boys and three girls photographed at the same chronological ages within sex; 12.75 years for girls and 14.75 years for boys. *From Tanner JM. Growth and endocrinology of the adolescent. In: Gardner L, ed.* Endocrine and Genetic Diseases of Childhood. *2nd ed., Philadelphia: W.B. Saunders.*

compared to the rather soft gracile outline of the pre-adolescent face. However, the maturity indicators that we use to assess maturation for clinical and research purposes are constrained by the fact that they must demonstrate "universality" - they must appear in the same sequence within both sexes - and similarity in both beginning and end stages. Because size is governed by factors other than the process of maturation, we cannot use an absolute size to determine maturation. While it is true in very general terms that someone who is large is likely to be older and more mature than someone who is small, it is apparent from Fig. 1.5 that as two such individuals approach each other in terms of age maturity distinction becomes blurred. We therefore use the appearance and *relative* size of structures rather than their *absolute* size to reflect maturity. The most commonly assessed maturity indicators are secondary sexual development, skeletal maturity, and dental maturity (see Chapter 12).

The control of growth

It is clear that the process of human growth and development is both complex and extensive. It is under the control of genetic, epigenetic, and environmental influences that operate in such a way that at specific times during the period of growth one or the other may be the dominant influence. At conception we obtain a genetic blueprint that includes our potential for achieving a particular adult size and shape. The environment will alter this potential. Clearly when the environment is neutral, when it is not exerting a negative influence on the process of growth, then the genetic potential can be fully realized. However the ability of environmental influences to alter genetic potential depends on a number of factors including the time at which they occur, the strength, duration, and frequency of their occurrence and on the age and gender of the child (see Chapters 8 and 9).

The control mechanism that environmental insult will affect is primarily the endocrine system. The hypothalamus or "floor" of the diencephalon situated at the superior end of the brain stem co-ordinates the activities of the neural and endocrine systems. In terms of human growth and development its most important association is with the pituitary gland that is situated beneath and slightly anterior to the hypothalamus. The rich blood supply in the infundibulum, that connects the two glands, carries regulatory hormones from the hypothalamus to the pituitary gland. The pituitary gland has both anterior and posterior lobes and it is the anterior lobe or "adenohypophysis" that releases the major hormones controlling human growth and development; growth hormone, thyroid stimulating hormone, prolactin, the gonadotrophins (luteinizing and follicle stimulating hormone), and adrenocorticotropic hormone (see Chapters 5 and 6). Normal growth is not simply dependent on an adequate supply of growth hormone but is the result of a complex and at times exquisite relationship between the nervous and endocrine systems. Hormones rarely act alone but require the collaboration and/or intervention of other hormones in order to

achieve their full effect. Thus growth hormone causes the release of insulin-like growth factor 1 (IGF-1) from the liver. IGF-1 directly affects skeletal muscle fibers and cartilage cells in the long bones to increase the rate of uptake of amino acids and incorporate them into new proteins and thus contributes to growth in length during infancy and childhood. At adolescence, however, the adolescent growth spurt will not occur without the collaboration of the gonadal hormones or sex steroids; testosterone in boys, and estrogen in girls.

There is ample evidence from research on children with abnormally short stature that a variety of environmental insults will disturb the endocrine system causing a reduction in the release of growth hormone. However, other hormones are also affected by insult and thus the diagnosis of growth disorders becomes a complex and engrossing series of investigations that increasingly requires an appreciation of both genetic and endocrine mechanisms (see Chapter 6).

Growth reference charts

The growth of François De Montbeillard was interesting not only because he depicts a normal pattern of growth but also because he achieved an adult height that was over 186 cm (6 ft 1in) and was quite tall for a Frenchman in the 18th century. How do we know that someone is "tall" or "short"? What criteria do we use to allow us to make such a judgment? Those not involved in the study if human growth will make such a judgment based on their exposure to other people. If, for instance, they have only lived among the pygmies of Zaire then anyone over 165 cm of 5 ft 5in would be very tall. If, on the other hand, they had only lived among the tall Nilotic tribesmen of north Africa then anyone less than 175 cm of 5 ft 9in would be unusually small. Most of us live in regions of the world in which the majority of people have adult heights that are between these extremes and view average adult heights at about 178 cm (5 ft 10in) for males and 164 cm (5 ft 5in) for females as being "normal." There is, of course, a range of adult heights about these average values and that range gives us an estimate of the normal variation in adult stature. Beyond certain points in that range we begin to think of an individual's height as being either "too tall" or "too short." This is also true of the heights of children during the process of growth. At any age from birth to adulthood there is a range of heights that reflects the sizes of normal children i.e. children who have no known disease or disorder that adversely affects height (e.g. bone dysplasias, Turner syndrome, etc.). In order to assess the normality or otherwise of the growth of children we use "growth reference charts." These charts depict both the average height to be expected throughout the growing years (typically from birth to 18 years), and the range of normal heights, in the form of percentile or "centile" distributions.

Fig. 1.6 is an example of such a reference chart. It depicts the normal range of heights for British boys from four to 18 years. The normal range is bound by outer centile limits of the 0.4th and 99.6th centiles. Thus "normal" heights are thought of as heights that fall between these limits although, of course, 0.8 % of normal children will have heights below the 0.4th centile or above the 99.6th centile (see Chapter 14). The illustrated centiles have been chosen because they each equate to about 0.67 Z-scores or Standard Deviation Scores (SDS) from the 50th centile or average values. Thus the 75th and 25th centiles are ±0.675 Z-scores above or below the mean, the 90th and 10th centiles are ±1.228 Z-scores and the 98th and 2nd centiles are ±1.97 Z-scores. Their importance is that not only do they provide a reasonable point at which to investigate possible abnormalities of growth but they also provide reasonable guidelines for how we expect growth to proceed within the normal range. It has been generally accepted that a child whose growth exhibits a movement of +0.67 Z-scores is exhibiting a clinically significant response to the alleviation of some constraining factor (see "catch-up" growth below).[15] Thus the movement of a child's height or weight upwards through the centiles from the 10th to the 25th or downwards from the 98th to the 75th can be viewed by clinicians as being more than simply a chance occurrence.

Children who do not have constraints upon their growth exhibit patterns of growth parallel to the centile lines prior to adolescence. However, as the adolescent growth spurt takes place they will depart from this parallel pattern and all adolescents will demonstrate "centile crossing." If they are "early developers" their height-for-age curve will rise through the centiles before their peers and level off early as they achieve their adult stature. "Late developers," on the other hand, will initially appear to fall away from their peers, as the latter enter their growth spurts, and then accelerate into adolescence rising through the centile lines when their peers have ceased, or nearly ceased growing. Even the child who enters their growth spurt at the average age for the population will cross centile lines. This is because the source data for these reference charts were collected in cross-sectional studies; studies in which children of different ages were measured on a single occasion. They thus reflect the average heights, weights, etc., of the population rather than the growth of an individual child. If one were able to undertake a growth study of the same children over many years (a longitudinal study) one could theoretically adjust the data so that it illustrated the adolescent growth spurt of the average child i.e. the child experiencing the adolescent growth spurt at the average age. In such a hypothetical situation the growth curve of the average child would fall exactly on the 50th centile line. But that is not the case with growth reference charts based on cross-sectional data; the average child will initially fall away from the 50th centile line as he/she enters the growth spurt and then cross it at the time of maximum velocity (peak velocity) before settling back onto the 50th centile as he/she reaches adult height.

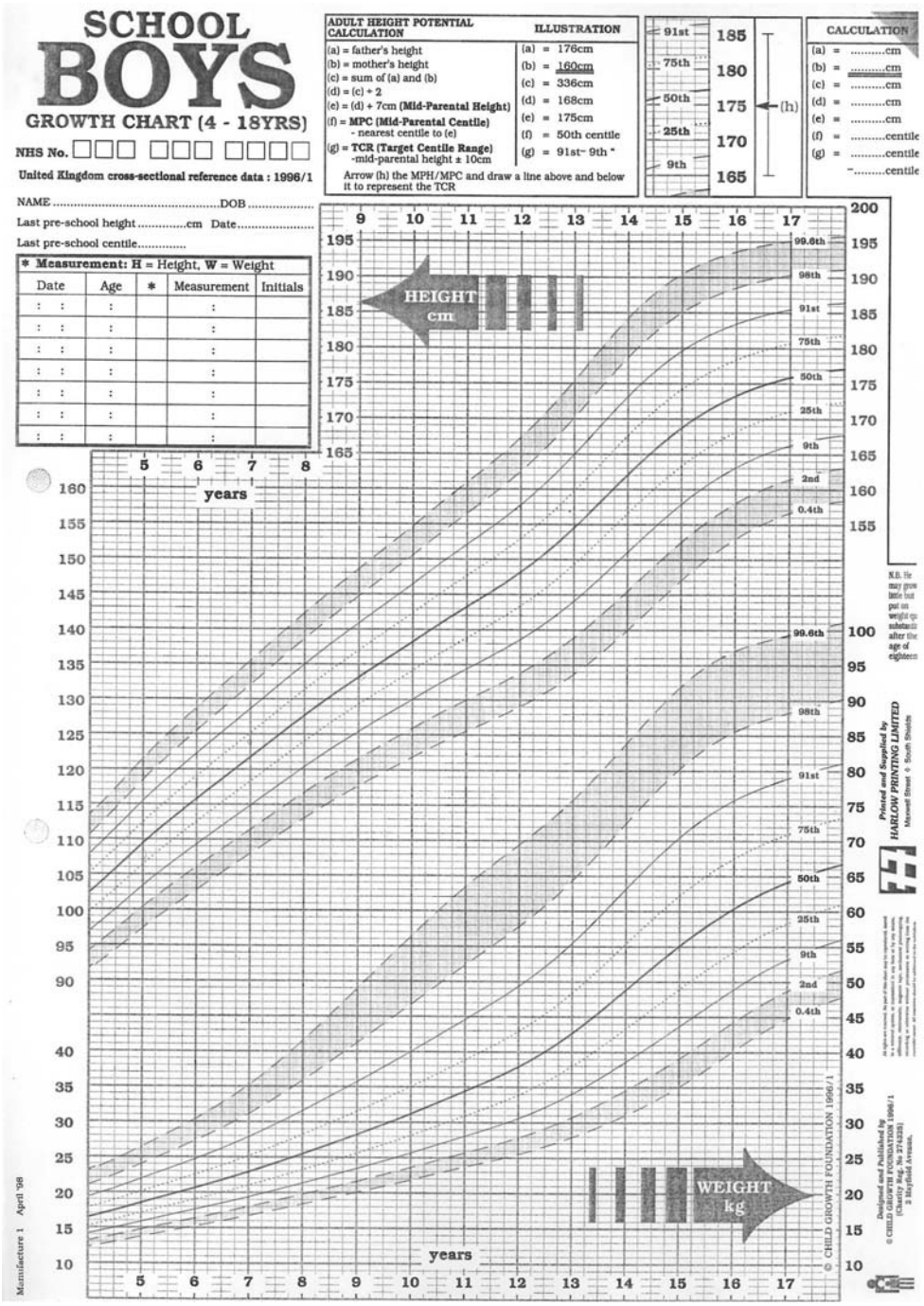

Fig. 1.6
Growth reference chart for UK males from four to 18 years (© Child Growth Foundation).

Fig. 1.7 illustrates the typical growth patterns exhibited by early, average, and late developers plotted on a clinical longitudinal growth standard (see Chapter 14). The early developing girl (E) accelerates into adolescence at about 8 years of age, some two years prior to the average, and rapidly crosses centile lines to move from just above the 50th to the 90th centile. However, her growth slows at about 13 years and her height centile status falls back to the 50th centile. Conversely the late developer (L) is almost 13 years old before she starts to accelerate and that delay causes her height centile status to fall from the 50th to below the 10th centile before rising to the 50th centile as she approaches adulthood. Finally, the average girl initially falls away from the 50th centile but then accelerates through it at the average age of peak velocity before following the 50th centile as adulthood is reached.

Canalization

Fig. 1.7 demonstrates more than simply the crossing of centiles by early and late developers. It also tells us something about the control of human growth. These are not hypothetical curves. They are the growth curves of real children who were measured on a 6 or 3 monthly basis throughout childhood and adolescence.[16] Note that during childhood they are growing on or near to the 50th centile and after the deviations brought about by their adolescent growth spurts they return to that same centile position in adulthood. Such adherence to particular centile positions is found time and again when one studies the growth of children. Indeed it is true to say that all children, when in an environment that does not constrain their growth, will exhibit a pattern of growth that is more or less parallel to a particular centile or within some imaginary "canal." This phenomenon was described by the British geneticist, C.H. Waddington (1905–75), in 1957[16] and has been termed "canalization" or "homeorrhesis." It is most likely that this pattern is genetically determined and that growth is target seeking in that we have a genetic potential for adult stature and the process of growth, in an unconstrained environment, takes us inexorably toward that target.

Catch-up growth

However, it is a truism to say that none of us have lived or been brought up in a completely unconstrained environment. Toward the end of our intrauterine life our growth was constrained by the size of the uterus. During infancy and childhood we succumbed to a variety of childhood diseases that caused us to lose our appetite and at those times our growth would have reflected the insult by appearing to slow down or, in the more severe case to actually cease.

Waddington[17] likens growth (or, as we now think of it, cellular decision making during growth) to the movement of a ball rolling down a valley floor. The sides of the valley keep the ball rolling steadily down the central course (point A in Fig. 1.8). If an insult occurs it tends to push the ball out of its groove or canal and force it up the side of the valley (point B). The

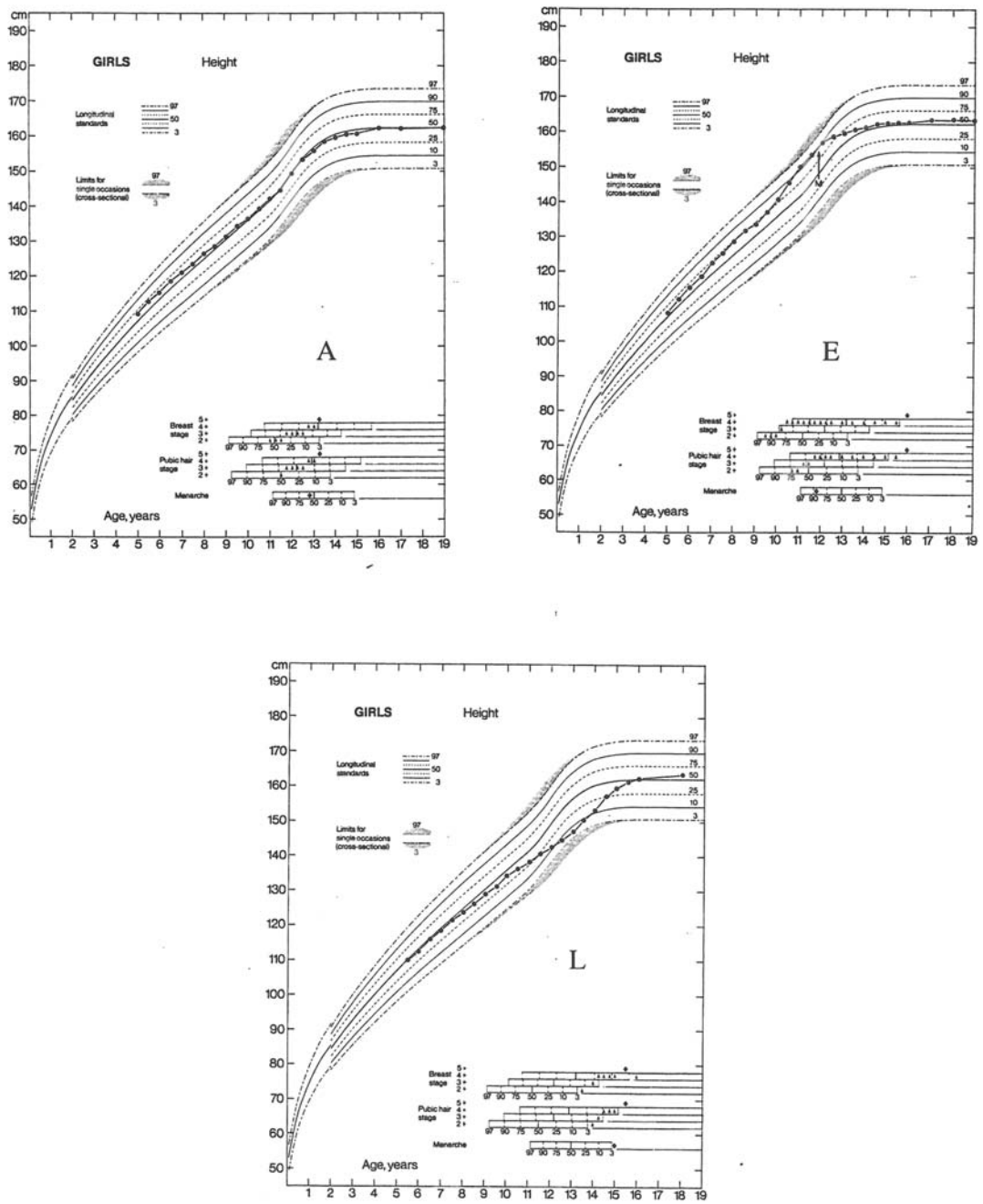

Fig. 1.7

Growth curves of early (E), Average (A) and Late (L) developers. *Data from numbers 35, 38, 45 in Tanner JM, Whitehouse RH.* Atlas of Human Growth. *London: Academic Press; 1980.*

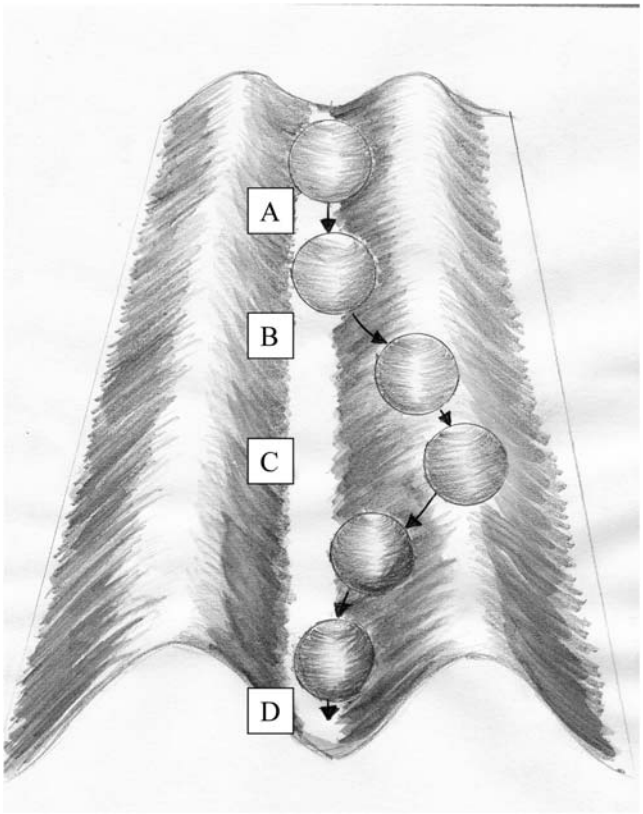

Fig. 1.8
An illustration of the phenomenon of canalization. A = normal canalized growth; B = the point at which an impact causes the ball to deviate up the side of the valley; C = the alleviation of the impact and a return to the valley floor; D = the resumption of normal canalized growth.

amount of deviation from the pre-determined pathway will depend on the severity and duration of the insult. However any insult will cause a loss of position and a reduction in growth velocity as the ball is confronted by the more severe slope of the valley wall. The magnitude of the loss of velocity will also depend on the severity and duration of the insult. Thus a small insult of short duration will cause a slight shift onto the valley sides which will entail a minor change in velocity. The alleviation of the insult will result in a rapid return to the valley floor at an increased velocity (point C). Having reached the floor normal growth velocity is resumed (point D).

This analogy may be seen to apply appropriately to the process of human growth. Fig. 1.9 shows the growth chart of a girl who has suffered from celiac syndrome.[16] In this condition there is an abnormality of the lining of the gut and food cannot be absorbed resulting in the child being starved. The result in terms of growth is that the height velocity is gradually reduced as the malnutrition becomes more and more severe. The

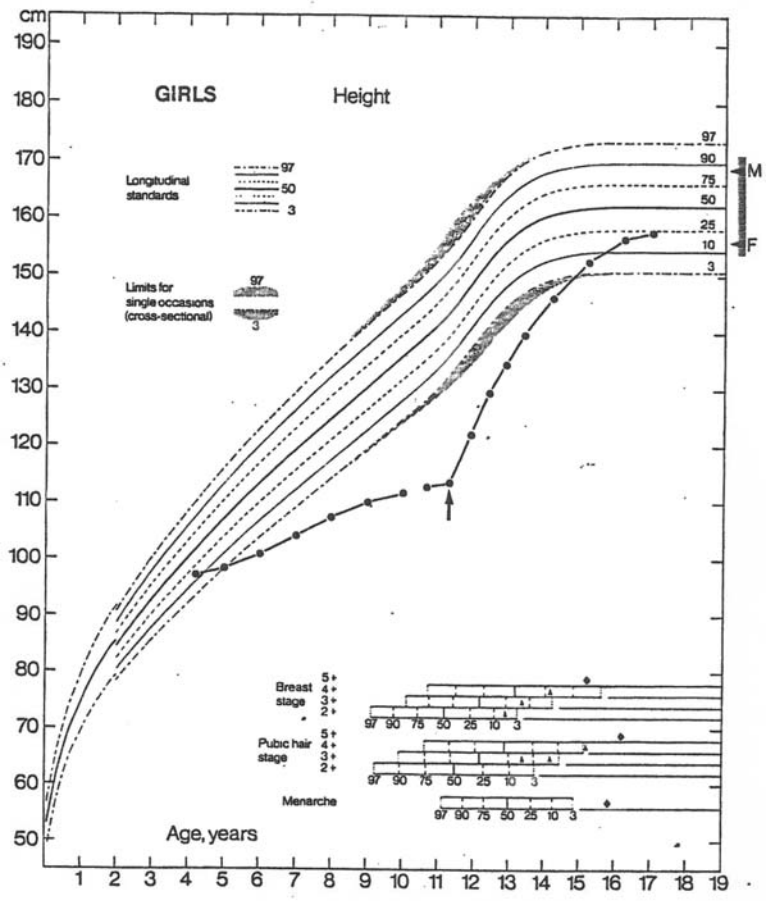

Fig. 1.9
Catch-up growth exhibited by a child with celiac syndrome. *Data from number 102 in Tanner JM, Whitehouse RH.* Atlas of Human Growth. *London: Academic Press; 1980.*

reduction in height velocity means that the height distance curve leaves the normal range of centiles and the child becomes abnormally short for her age. So, at the age of almost 12 years she is the average height of a 5-year-old. On diagnosis the child is switched to a gluten-free diet which alleviates the malabsorption. Recovery of height velocity is rapid and jumps from 1 cm yr^{-1} to 14 cm yr^{-1} returning the child to the normal range of centiles within three years. Indeed this girl ends up within the range of heights one would expect given the heights of her parents. So she demonstrates "complete" catch-up growth in that she returns to the centile position from which she most probably started.

Catch-up growth is, however, not always complete and appears to depend on the timing, severity and duration of the insult. This appears to be particularly true in the treatment of hormone deficiencies. Initial diagnosis is often delayed until the child is seen in relation to

other children and the deficiency in stature becomes obvious. Usually a hormone deficiency, e.g. growth hormone deficiency, is also accompanied by a delay in maturation. Response to treatment appears to depend on some pre-treatment factors such as chronological age, height, weight and skeletal maturity i.e. on how long the child has been deficient, and how severe the deficiency in height and weight are and by how much the maturity has been affected.

Summary and conclusions

This chapter forms an introduction to the study of human growth and development.

The curve of human growth has been a changing characteristic of our genus as we have evolved over the last 2 million years. It has changed in duration and magnitude as we have been freed of the environmental constraints that have affected us throughout our evolution but its major characteristics have remained unaltered. That curve reflects two major stages during which adjustment to final size and shape are the direct consequences. Infancy and adolescence are times of adjustment and assortment. More than 50% of infants exhibit either catch-up or catch-down growth during the first two years of life.[15] These adjustments have long term consequences in terms of final size, shape, morbidity, and perhaps mortality. The timing of the adolescent growth spurt, its magnitude, and duration are also fundamentally important in terms of healthy and successful survival. The biological phenomena of canalization and catch-up growth dictate the magnitude, duration and ultimate success of these alterations and adjustments.

No one would argue that environmental constraints on growth through the processes of famine and disease have not been constant influences, not only on our survival, but also on our size and shape at any age. The past millennia of environmental insult have resulted in the survival of representatives of the species *Homo sapiens* who are adapted and adaptable to their environment. We are the survivors and as such we use survival strategies to ensure that we continue the species. One of the most powerful of these strategies is the plasticity of our growth and development. Throughout the following chapters you will learn how that plasticity is inherited, controlled, and expressed — it is a fascinating story about the most fundamental biological phenomena of our species.

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Suggested readings

Alder K. *The Measurement of all Things*. New York: The Free Press; 2002.
A fascinating account of the development of a uniform system of measurement against the background of revolutionary France and the acceptance of arbitrary systems of measurement resulting from papal and monarchial dictates.

Bogin BA. *Patterns of Human Growth*. 2nd ed. Cambridge: Cambridge University Press; 1999.
Barry Bogin's landmark volume on the patterns of human growth is a personal journey through the bicultural approach to human growth and development. It is well written and accessible and is an extremely useful additional reference text. The 3rd edition is due to be published in 2021.

Thompson D'AW. In: Bonner JT, ed. *On Growth and Form*. Abridged ed. Cambridge: Cambridge University Press; 1961.
D'Arcy Thompson's classic volume in an abridged and thus accessible form. None of the poetry of Thompson's writing has been lost in this edition and for the serious scholar of human biology this is an important volume.

Tanner JM. *Fetus into Man Cambridge Mass*. Harvard University Press; 1990.
Fetus into Man was the first of Jim Tanner's volumes aimed at a general audience rather than at human biologists. It explains physical growth and development from birth to adulthood precisely and elegantly and as a general book for background reading it is invaluable.

Tanner JM. *A History of the Study of Human Growth*. Cambridge: Cambridge University press; 1981.
An historical account of the study of human growth which will be of interest to post-graduate students wishing to understand the context within which the growth of children has become a core aspect of human biology, education, psychology, sociology, pediatrics, and economic development.

Internet resources

http://www.buffon.cnrs.fr/ A French Website Providing Access to Histoire Naturelle.
There are a variety of websites that provide a wealth of information on human growth and development. However, it is very important to distinguish between the types of information required before accepting the text of any particular site. Many are concerned primarily with psychological, emotional or social development and include little or no physical development. Others relate to growth disorders or clinical aspects of growth and yet others are aimed at parents. It is always important to rigorously check the provenance of the website and ensure that it is from a reputable scientific institution.

CHAPTER 2

Prenatal and infant growth

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Introduction

The first 1000 days, representing the period between conception and a child's second birthday, is recognized as a critical period that influences lifelong health and wellbeing. A fundamental reason for this is because it is during this period that growth and development are at their most rapid. The developmental origins of health and disease (DOHaD) paradigm, pioneered by David Barker toward the end of 20th century, led to an explosion of research investigating the long-term outcomes associated with poor growth during gestation and infancy. Much of this early work (originally referred to as the "fetal origins hypothesis") was based on measures at birth, typically birth weight, as a proxy for fetal growth. Assessing fetal growth in such a way not only masks the pattern of growth that has occurred in fetal life, i.e. various growth trajectories can ultimately result in the same size at birth, but also lacks consideration of critical periods of growth during gestation. With the increasing utilization of ultrasonography into routine antenatal care and research studies, we are now able to directly assess patterns of fetal growth across the entire gestational period, to produce charts of fetal size and growth, and to investigate how fetal growth is related to later outcomes.

After 40 weeks of gestation, the infant leaves the relatively stable environment experienced in utero and enters the more volatile postnatal environment. Infancy is a high velocity but rapidly decelerating phase of growth; in the first month after birth male and female infants show average increases in weight of 1023 g/month and 879 g/month, respectively, which decreases to 239 g/month and 232 g/month by the 12th month. During this period the genes regulating growth become more influential and it is typical to observe substantial shifting of centiles (upwards and downwards) when plotted on distance charts, as infants try to achieve their genetically determined growth "canal". Historically, these instances of rapid infant growth were considered a natural response to growth constraint experienced in utero. Indeed, such growth in linear dimensions has protective benefits for the infant, particularly in low- and middle-income countries (LMICs). More

Human Growth and Development. https://doi.org/10.1016/B978-0-12-822652-0.00021-3

recently, especially in high income countries (HICs), focus has shifted to the epidemiology of "rapid infant weight gain" and numerous studies have observed associations between rapid infant weight gain and future adiposity and cardiometabolic risk factors, regardless of size at birth. Indeed, it is the accumulation of such findings that led to the shift from the "fetal origins" paradigm to the more encompassing "developmental origins" model, acknowledging the critical importance of growth in both the fetal and infant periods.

Periods of gestation

It is convention to refer to the intrauterine period as trimesters, splitting the 37–41 week duration of a term pregnancy, into approximately three 13–14 week intervals. In terms of development, the first trimester corresponds broadly to "embryogenesis", with the period thereafter referred to as the "fetal" stages of development.

Embryonic period ("embryogenesis")

Pre-implantation stage

Fertilization of the female ovum is most likely to occur within 12–24 h of when it is released (ovulation), which typically occurs midway through the menstrual cycle (i.e. 14 days after a females last period). As sperm is able to live inside the female reproductive tract for up to five days, intercourse within the five days preceding ovulation or on the day of or after ovulation will increase the chances of fertilization occurring.

Immediately after fertilization, the single-celled zygote begins to undergo cell division. Approximately 3 days after fertilization, the 16-cell conceptus has traveled down the Fallopian tubes into the uterus. Once inside the uterus, cell division continues and the ball of approximately 100 tightly bound cells, now referred to as a blastocyst, begin to organize themselves around a fluid-filled cavity known as blastocoel. Within this cavity, a collection of cells forms into an inner cell mass which will ultimately develop into the embryo. Other components of the blastocyst (trophoblasts) will develop into the chorionic sac and the fetal portion of the placenta.

Implantation

Starting around the end of the first week, the blastocyst adheres to the wall of the uterus (endometrium) and via the trophoblast cells, begins to implant itself. Upon successful implantation, the superficial cells of the trophoblast join together to form the syncytiotrophoblast, which digest endometrial cells to secure the blastocyst into the uterine wall. The syncytiotrophoblastic cells then secrete human chorionic gonadotropin (hCG), a hormone signaling the ovary to continue its production of progesterone and estrogen in order to preserve the uterine lining and prevent menstruation. The increased production of

hCG leads to accumulation in the maternal bloodstream which is ultimately excreted in the urine. It is the detection of this elevated level of hCG in maternal urine which forms the basis of the commonly-used home based pregnancy tests. Implantation is typically complete by the middle of the second week.

Embryonic development

After implantation is achieved, cells from the inner cell mass begin to fold into a two-layered disc, composed of the epiblast (upper layer) and hypoblast (lower layer). In addition, other cells from the inner cell mass begin to form some of the extra-embryonic tissue that provide protection and nourishment for the developing embryo: the amnion, the yolk sac, the allantois and the chorion (see Fig. 2.1 below).

Gastrulation occurs in week three of development, a process in which growth factors direct cells to multiply and migrate to transform the two-layered disk into the three definitive germ layers: endoderm (displacing the hypoblast), mesoderm and ectoderm (displacing the epiblast) (see Fig. 2.2 below).

These germ layers will go on to develop into specific structures in the developing embryo: the endoderm ultimately developing into the epithelial lining of the lungs, gastrointestinal tract, liver and pancreas; the mesodermal cells becoming the skeleton, muscles, connective tissues as well as major organs including the heart and kidneys; while the ectoderm differentiates into cells within the central (CNS) and peripheral nervous systems (PNS), sensory organs, epidermis, hair and nails.

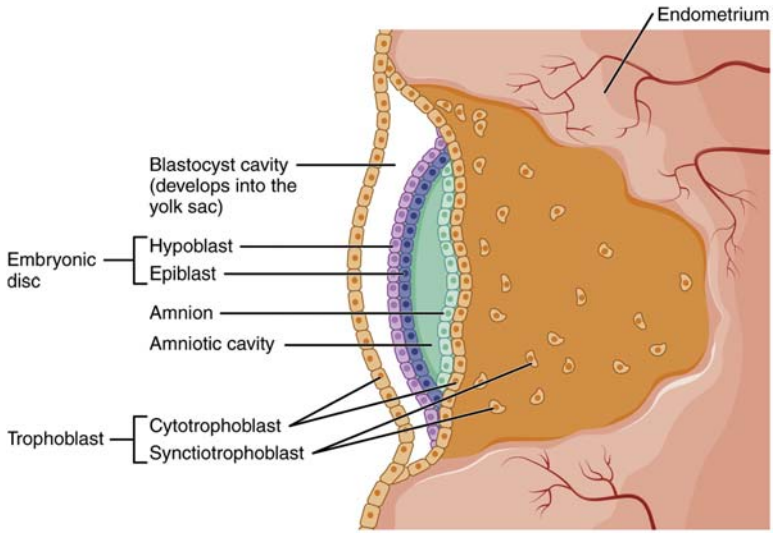


Fig. 2.1
Formation of the embryonic disc.

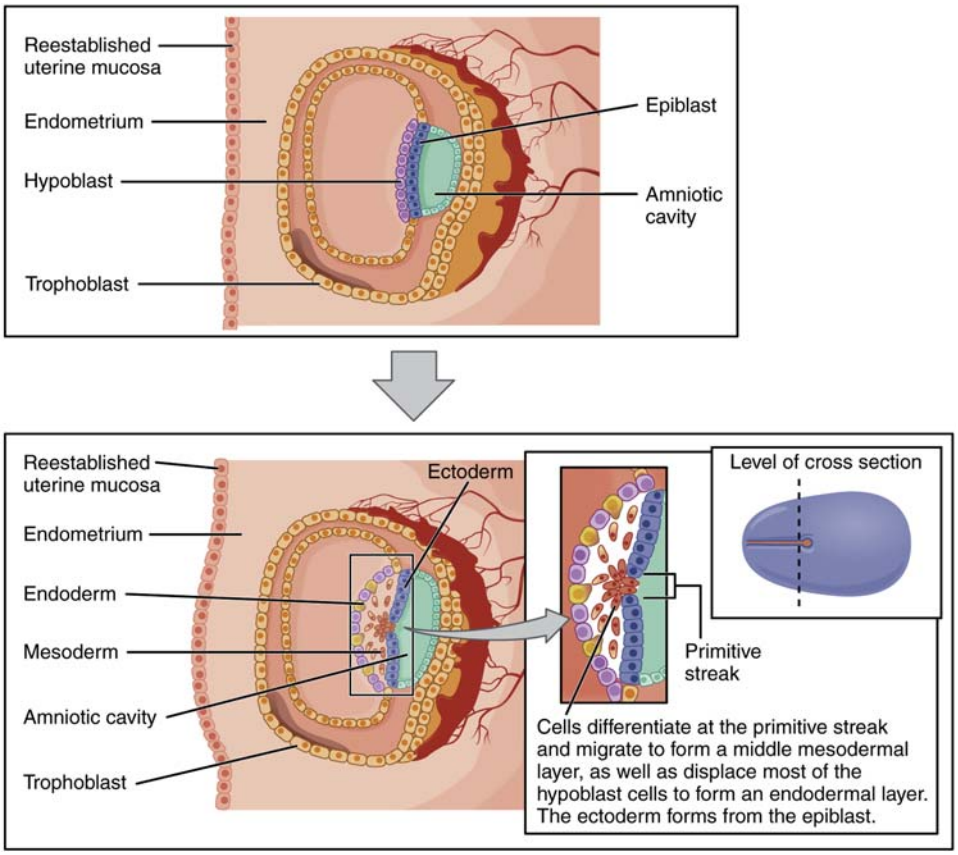


Fig. 2.2
Formation of the three primary germ layers.

The development of the CNS from the ectodermal cells begins shortly after gastrulation, in a process called neurulation. During this process, which occurs in weeks three to four of development, thickening of the ectodermal cells gives rise to the neural plate, which then begins to fold upward to form a neural tube. The anterior part of the neural tube then subdivides into vesicles that will ultimately develop into the brain structures (see Fig. 2.3 below).

Folate is critical for the healthy development of the neural tube and a folate deficiency in early pregnancy can lead to the development of a number of serious birth defects known as "neural tube defects", examples of which include spina bifida and anencephaly. Spina bifida is a birth defect in which the vertebral column is open (bifid) as a result of a failure of the spinal neural tube to close at the caudal end. Spina bifida is one of the most common congenital malformations globally, occurring in around 1 in 1000 births.[1]

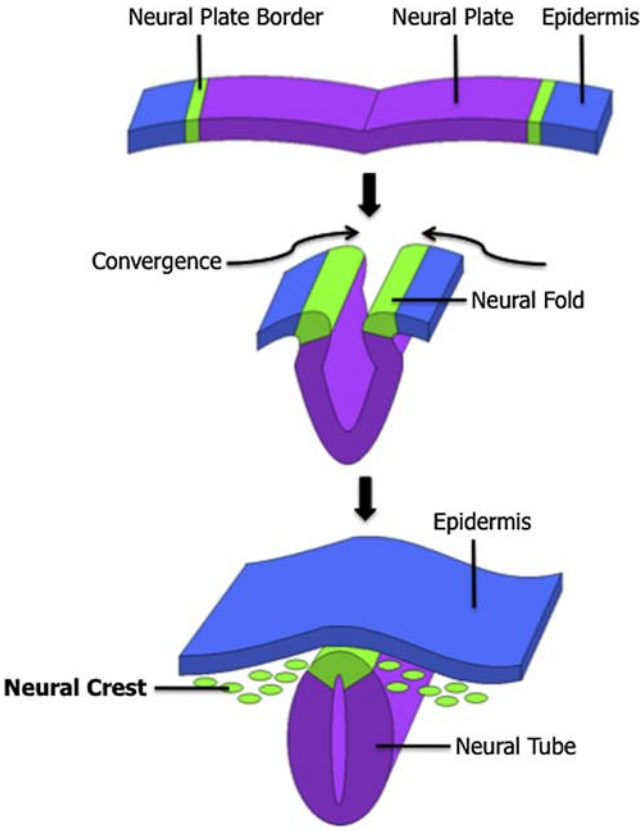


Fig. 2.3
Formation of the neural tube via neurulation.

Anencephaly is also a failure of the neural tube closing, but at the other end (cranial end). A consequence is that large portions of skull (calvarium) and brain tissue do not develop. It is less common than spina bifida, but the prognosis is much poorer. In light of this, current guidance from the United Kingdom National Health Service recommends that pregnant women and women trying to conceive should take a 400 mg daily dietary supplement of folic acid until the 12th week of gestation, in order to reduce the risk of the fetus developing a neural tube defect.

Organogenesis, the process by which organs begin to develop their basic structures from the three germ layers, also commences shortly after gastrulation, during the third week. The heart is the first organ to develop and a heartbeat is usually detectable in the fourth week of gestation. During the fourth and fifth weeks the liver, pancreas, spleen and gallbladder all begin to form. In addition to this organogenesis, the fourth and fifth weeks

signals the development of the eye pits and limb buds. In weeks 6 and 7 the kidneys, stomach and lungs begin to develop, while fingers and toes begin to form via the process of apoptosis (causing tissue between fingers and toes to disintegrate).

By the end of the eighth week, representing the final week of the embryonic period, all essential organs have begun to develop. External genitalia are evident, however it is still too early to distinguish between male and female embryos. At the end of the embryonic period, the embryo is around 20−30 mm in length, of which the head constitutes around 50%, and weighs approximately 8 g.

Fetal development

From the ninth week of gestation, typically when all gross organs have at least started to develop, and extending until birth, the developing offspring is referred to as a fetus. The fetal period is characterized by cell hypertrophy and hyperplasia, processes which develop the structures and functions of the immature organ systems which began their development in the embryonic period.

In terms of gross fetal growth, the second trimester may be marked by rapid increases in length (measured as the distance from crown-to-rump (CRL)), increasing from approximately 9 cm at the start (12−13 weeks approximately) to around 23 cm at the end (26 weeks approximately). Tanner[2] reported that the timing of peak length velocity was around 16−20 weeks gestation and support for this has been seen in subsequent studies, with Bertino et al.[3] who observed peak femur diaphysis occurring at 20 weeks, and more recently from Grantz et al.[4] who estimated peak velocity in linear dimensions (femur length (FL) and humerus length (HL)) occurring at around 15−16 weeks gestation, decreasing thereafter. Alongside these increases in linear growth, significant development of the sensory organs also occurs in the early part of the second trimester, particularly of the eyes and ears, which begin to move to their final anatomical positions.

If the second trimester is characterized by increases in length, then the third trimester represents the period of substantial increases in weight. Subcutaneous fat deposition constitutes a large proportion of this weight gain, causing the previously wrinkled skin to fill out and soften. The increased fat stores serve as both a source of energy and insulation in the immediate extrauterine environment, in which the thermoregulation and nutrient supply previously received from the mother have been removed. Fetal weight typically increases at a constant rate (linearly) up until the final few weeks of gestation, during which the rate plateaus. This growth pattern culminates in average birth weights for full term males and females of 3.3 kg and 3.4 kg, respectively,[5] though geographical variation is apparent, as observed in Table 2.1. The corresponding values for length (now measured from head-to-toe not crown-to-rump) are 49.9 cm and 49.2 cm, respectively.[5]

Table 2.1: Variation in term[a] birth weight and length across 8 countries included in the Intergrowth 21st study.[5]

	Country							
	Brazil	**China**	**India**	**Italy**	**Kenya**	**Oman**	**UK**	**USA**
Birth weight (kg)	3.3 (0.4)	3.4 (0.4)	2.9 (0.4)	3.3 (0.4)	3.3 (0.4)	3.1 (0.4)	3.5 (0.5)	3.4 (0.5)
Birth length (cm)	49.0 (1.7)	49.7 (1.6)	48.6 (1.8)	49.4 (1.7)	49.1 (1.8)	49.0 (1.8)	49.9 (1.9)	49.9 (2.2)

[a]Term indicates all babies born at 37 weeks' gestation or later. Sexes combined.

Assessing growth during pregnancy

Ultrasonography

Prior to the incorporation of ultrasonography into standard obstetric care, fetal growth was assessed using data collected from pre-term fetuses, whether this be naturally occurring preterm births or abortions.[2] The use of expelled infants of varying gestational ages for the assessment of fetal growth is, however, methodologically flawed. As severe preterm or aborted births are a manifestation of various pathological states generally associated with reduced growth, e.g. an abnormal in utero environment; congenital abnormalities; or acquired infections, using such infants provides biased information on the growth pattern in utero. This is even the case for otherwise healthy late-preterm births, as it has been shown that the assumption that fetal growth in full and preterm fetuses follows the same pattern is questionable.[6,7]

A commonly used clinical measure to assess fetal size and growth is the Symphysis Fundal Height (SFH), measured from the top of the fundus to the upper border of the symphysis pubis. In the United Kingdom (UK), this measurement is still advocated by the National Institute of Health and Care excellence (NICE) from 24 weeks onwards.[8] However, the accuracy of SFH in the detection of the SGA fetus has been questioned[9] and accuracy in uncomplicated pregnancies is also reduced as a result of poor inter- and intra-observer reliability.[10–12] Furthermore, SFH measurements become less reliable in later gestation due to the descent of the fetus into the maternal pelvis.[13]

In comparison, ultrasonography is able to provide accurate estimates of various biometric dimensions (2-dimensional and 3-dimensional) necessary for assessing size and growth as well allowing the sonographer to visually identify any structural abnormalities that may occur. Additionally, ultrasound is a non-invasive tool which consequently minimizes harm to the mother and fetus.[14] As such, and paired with the limitations of the techniques reported above, ultrasonography is regarded as the optimal method for assessing fetal size and growth, with Haas stating that ultrasonography is the only "direct safe method of measuring the growing fetus in utero".[15]

In the UK women should be routinely offered two ultrasound scans during gestation.[8] The first of these, the "Dating scan" should be offered between 10 weeks 0 days and 13 weeks 6 days. As the purpose of this scan is to determine gestational age, measurements of fetal size are not recorded, other than that required for calculating gestational age (see next section). The second routine scan, the "Anomaly Scan" is offered between 18 weeks and 0 days to 20 weeks and 6 days. As the name implies, the purpose of this scan is to check for a range of structural anomalies in the fetus which are either incompatible with life, may benefit from antenatal treatment, or which require immediate postnatal support.[16] At this scan, head circumference (HC), abdominal circumference (AC) and FL are measured and estimated fetal weight (EFW) is calculated. In the UK, third trimester ultrasound scans are not routinely offered to low risk pregnancies, but gravidas deemed to have a higher risk pregnancy are offered further scans for increased surveillance.

Assessing gestational age

Antenatal care relies on an accurate assessment of the age of the fetus.[17] Two distinct but often conflated terms referring to the age of the fetus are gestational age and conceptional age. Conceptional age is the age of the fetus since the time of conception, whereas gestational age is the age since the last menstrual period (LMP), which on average occurs two weeks prior to ovulation. Gestational age therefore is two weeks longer than conceptional age. As most women do not know when ovulation occurred (and thus conception), but are more likely to recall their LMP, the convention is to refer to the age of a fetus in terms of gestational age.

While LMP is used as the basis for gestational age calculation, ultrasonography has been advocated as the optimal practice for assessing gestational age. This is because of the known problems encountered when using last menstrual period (LMP) to date pregnancy, such as unreliable recall and variations in the follicular phase of the ovulatory cycle,[18–21] paired with findings reporting equal/greater predictive abilities for onset of labor using ultrasound measurements.[19,22,23] During the first trimester "dating scan", the CRL is measured and using the formula proposed by Robinson and Fleming,[24] matched to corresponding gestational ages. An important assumption underpinning the use of fetal biometry in the assessment of gestational age is that variation between fetuses throughout the dating period is negligible. Recent studies have however reported, that this assumption may not be valid, with first trimester CRL and change in CRL showing associations with various maternal (age, diastolic blood pressure, hemoglobin level, hematocrit level, folic acid supplementation), fetal (sex) and both fetal and maternal (ethnicity) factors.[25–28] Such variability in the growth rate of CRL during the first trimester casts doubts on its

suitability as a dating tool. Conversely, others have concluded that charts based on CRL in White participants[29,30] are applicable in different populations and Pemberton et al. in their appraisal of first trimester fetal biometry, state that "CRL is still the most accurate fetal measurement in the first trimester and that these dating curves are applicable across populations".[31] As such, gestational age assessment using CRL remains the standard practice internationally.[32,33]

Recently, DNA methylation has been used to accurately estimate gestational age at birth,[34,35] leading to the concept of "epigenetic gestational age". While these DNA methylation signatures have been obtained from cord blood and thus cannot predict gestational age in advance, there is optimism that by utilizing fetal cells in the maternal circulation, a similar method may eventually enable actual prediction of gestational age and the due date in pregnant women. In the meantime, epigenetic gestational age represents a molecular marker of gestational age which could provide additional information when clinical estimates are unavailable or unreliable, e.g. in women who are unsure of the date of their last menstrual period, or did not have ultrasounds performed in early pregnancy.

Assessing growth using fetal biometry

Commonly used fetal biometry parameters for assessing fetal growth are head HC, AC and FL. While bi-parietal diameter (BPD) is often recorded, it's use for both estimating gestational age and assessing the appropriateness of fetal size is not recommended in the United Kingdom (UK), as this dimension is dependent on the shape of the head.[36]

Once obtained (see[32] for measurement guidelines), these dimensions can then be compared to the respective growth distance or velocity reference (e.g. [4,37–39]) or standard (e.g. [40]). For example, Figs. 2.4–2.8 show the average velocity curves, by ethnic group, for fetal AC, BPD, FL, HC, and HL, from the US-based National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies.[4]

In addition, these dimensions can be used to obtain an estimated fetal weight (EFW). A number of formulas exist for the estimation of fetal weight (see[41] for a review of these). No formula is able to estimate fetal weight exactly, and the amount of error has been shown to vary depending on the formula used and across the gestational age and weight distributions. However, the most commonly used EFW formula and the one used in the recently published World Health Organization EFW standards,[42] is that developed by Hadlock et al.[43] the formula for which is:

$$\mathrm{Log}_{10}\mathrm{Weight} = 1.326 - 0.00326\mathrm{AC} \times \mathrm{FL} + 0.0107\mathrm{HC} + 0.0438\mathrm{AC} + 0.158\mathrm{FL}$$

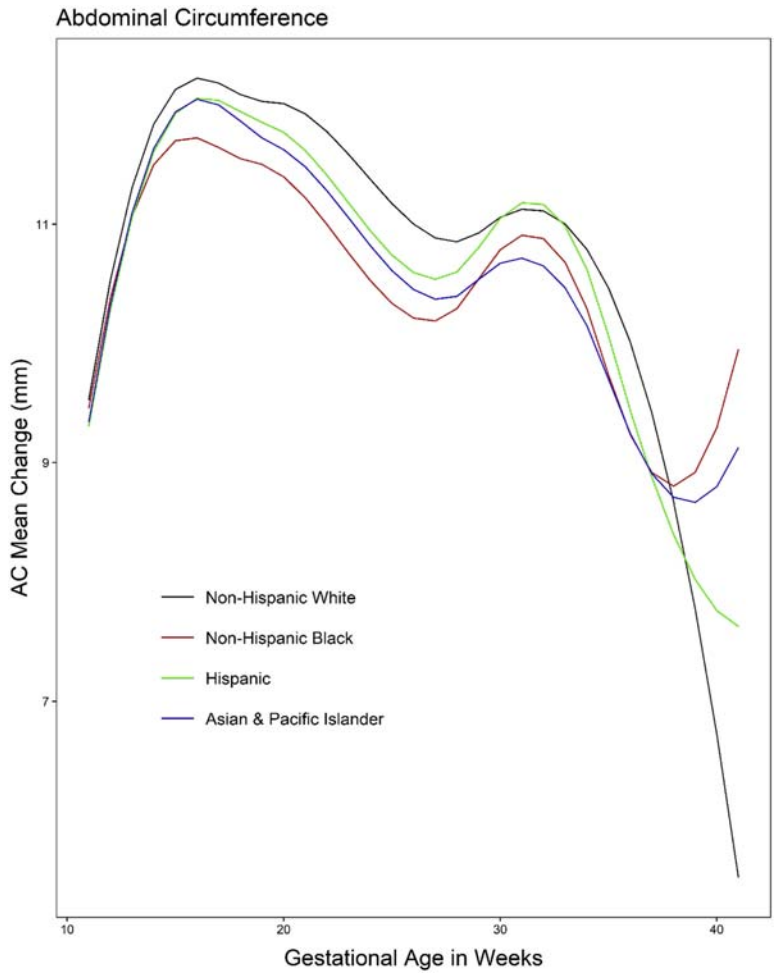


Fig. 2.4
Fetal abdominal circumference velocity (mm/week) by ethnicity and gestation. *Grantz, et al. Fetal growth velocity.* Am J Obstet Gynecol. *2018.*

Fetal weight charts

Fetal weight standards

Traditionally, this EFW will then be compared to size-for-gestational age referent data to assess the adequacy of fetal growth (or specifically, size), with a weight between the 10th-90th, 5th-95th or 3rd-97th centiles often considered appropriate-for-gestational age. Several ultrasound-based fetal weight references have been published,[6,44–47] typically based on locally derived data from high income countries (HICs) and thus providing uncertain applicability in a world of ethnic variation. Even within similar populations, the

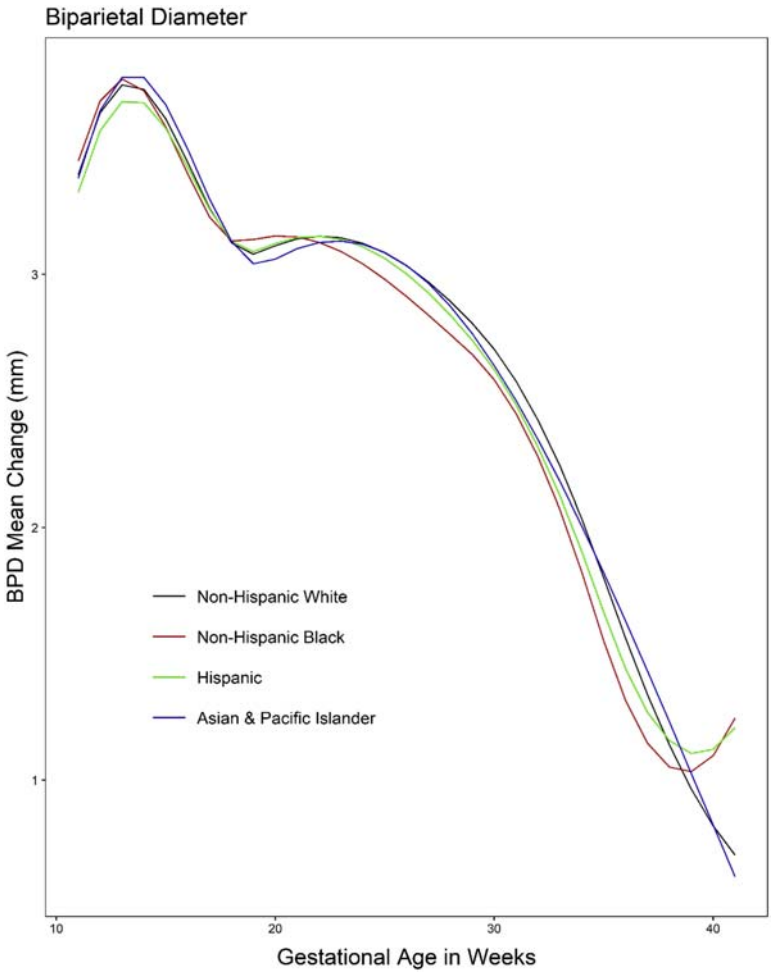


Fig. 2.5
Fetal biparietal diameter velocity (mm/week) by ethnicity and gestation. *Grantz, et al. Fetal growth velocity.* Am J Obstet Gynecol. *2018.*

availability of such a range of charts each with their own inclusion criteria creates inconsistency in diagnostic decision-making and the potential to cause undue anxiety to expectant mothers.

In an attempt to address these issues, three longitudinal cohort studies were recently undertaken to create international fetal weight standards: the Intergrowth 21st project,[40,48] the World Health Organization (WHO) Multicentre Growth Reference Study (WHO Fetal)[42] and the National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies.[4,49] The Intergrowth 21st and WHO fetal studies both set out with the assumption that there would be no differences internationally in fetal growth when

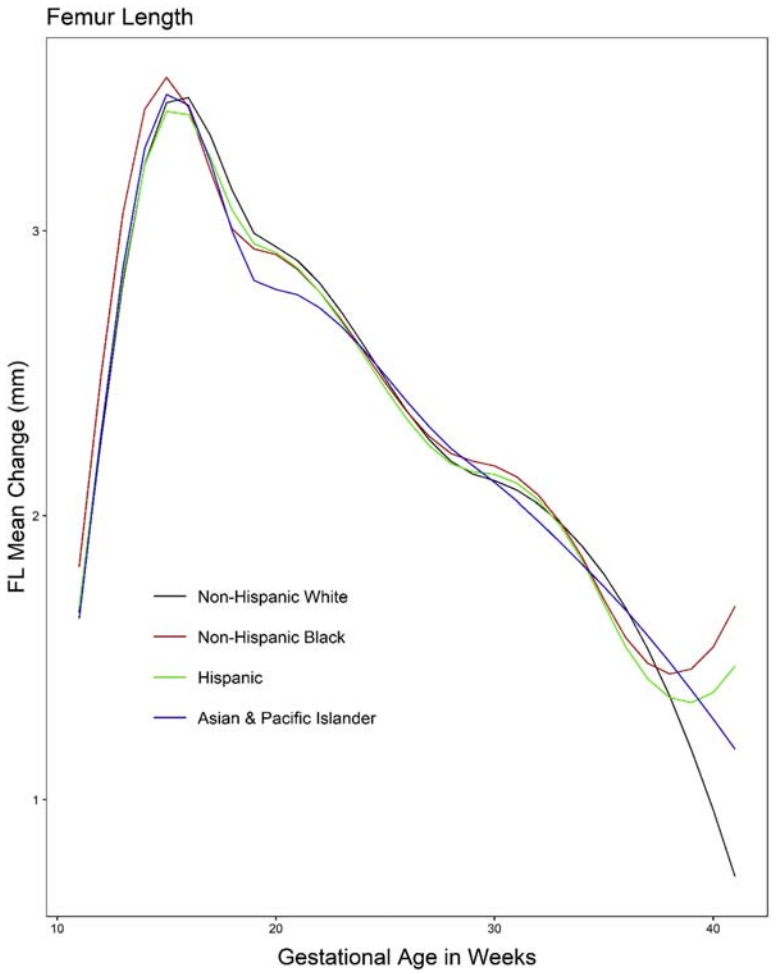


Fig. 2.6
Fetal femur length velocity (mm/week) by ethnicity and gestation. *Grantz, et al. Fetal growth velocity.* Am J Obstet Gynecol. *2018.*

conditions were optimal and thus the aim of both studies was to create a single fetal growth standard that could be used universally. The aim of the NICHD fetal growth studies was to identify whether ethnic-specific fetal growth standards were needed, in recognition of the fact that because fetal weight is commonly estimated from AC, HC and FL, in which there are known differences in children and adults of differing ethnic groups, separate standards might be necessary to capture optimal growth and more precisely estimate fetal weight. In summary, despite all three studies having extensive inclusion and exclusion criteria aimed at selecting healthy women with uncomplicated pregnancies to enable optimal fetal growth, none of the three studies observed consistent standards for

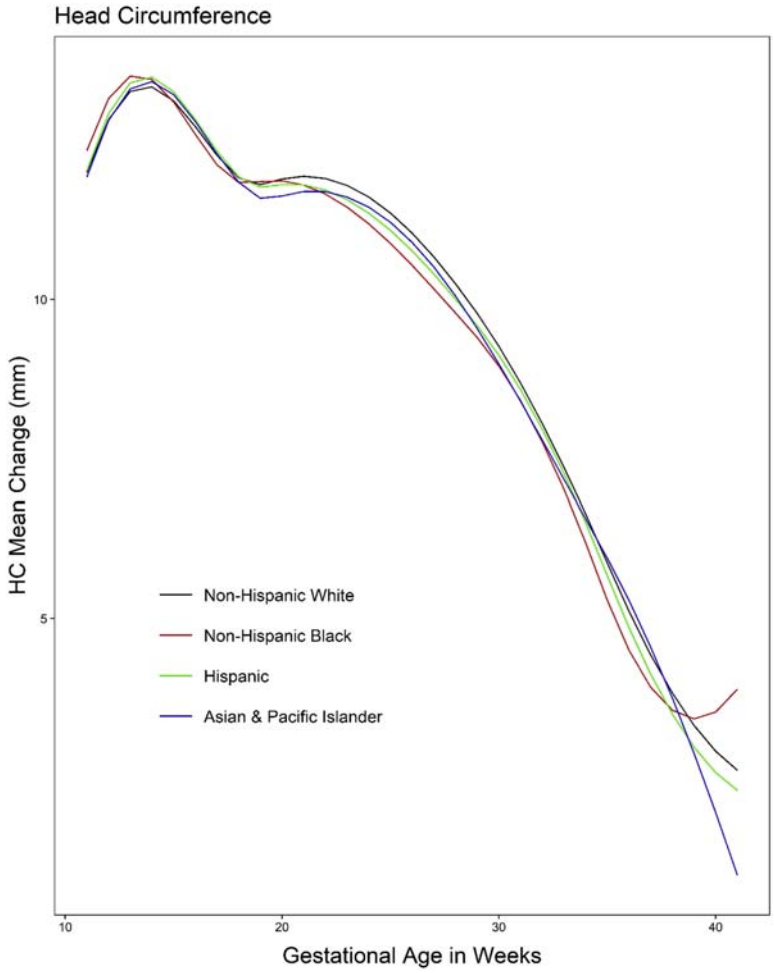


Fig. 2.7
Fetal head circumference velocity (mm/week) by ethnicity and gestation. *Grantz, et al. Fetal growth velocity.* Am J Obstet Gynecol. *2018.*

population subgroups. The Intergrowth 21st study did not formally test for differences in the EFW centiles between the constituent study sites (Brazil, Italy, Oman, UK, USA, China, India and Kenya) as prior analyses suggested minimal variation in other fetal growth parameters[40,50] and thus supported pooling of all study sites. However, formal testing of the differences was not done and only differences in CRL and HC, which are known to display less variation than other fetal parameters, were explored. By comparison, the WHO Fetal study also had the objective to create a single fetal weight standard, but upon observing significant ethnic and cultural differences between study sites (Argentina,

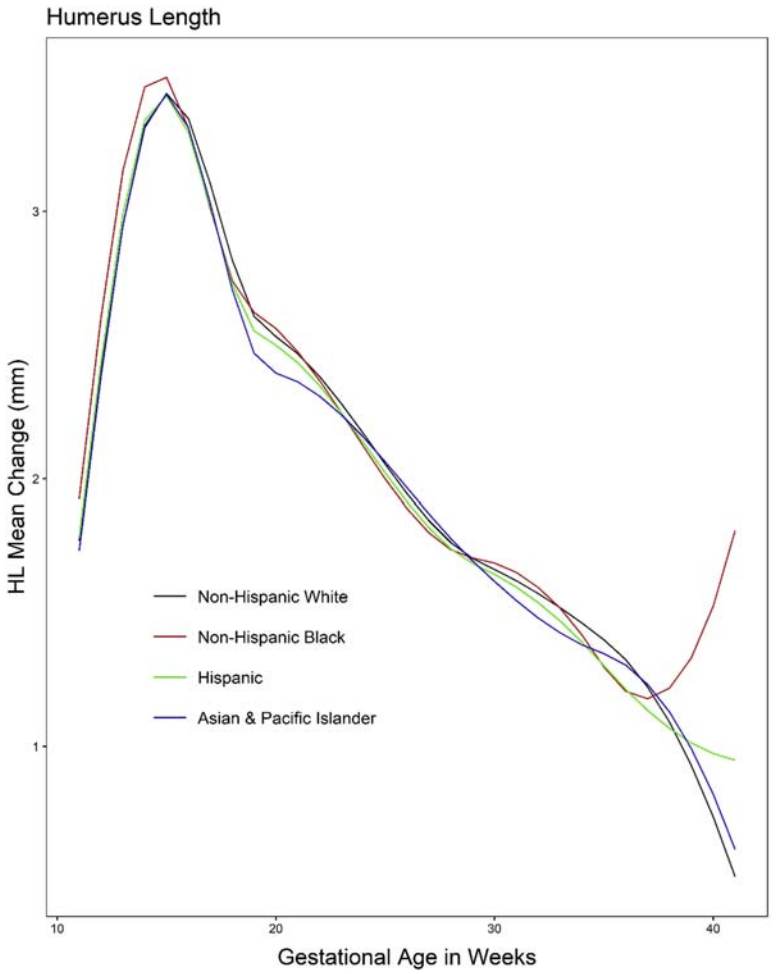


Fig. 2.8
Fetal humerus length velocity (mm/week) by ethnicity and gestation. *Grantz, et al. Fetal growth velocity.* Am J Obstet Gynecol. *2018.*

Brazil, Democratic Republic of Congo, Denmark, Egypt, France, Germany, India, Norway, and Thailand), concluded that even under optimal maternal conditions, fetal growth is not uniform. As such, they have not labeled their charts as "standards". A plot of the WHO EFW curves, for both males (blue) and females (red) can be seen in Fig. 2.9. Finally, the NICHD Fetal Growth Studies observed comparable differences between ethnic groups to the country level differences observed in the WHO Fetal study, with the authors arguing for ethnic specific fetal growth standards. Taken together, the results of the three studies suggest that there is no single fetal growth standard which is equally applicable for all pregnancies across the world.[51]

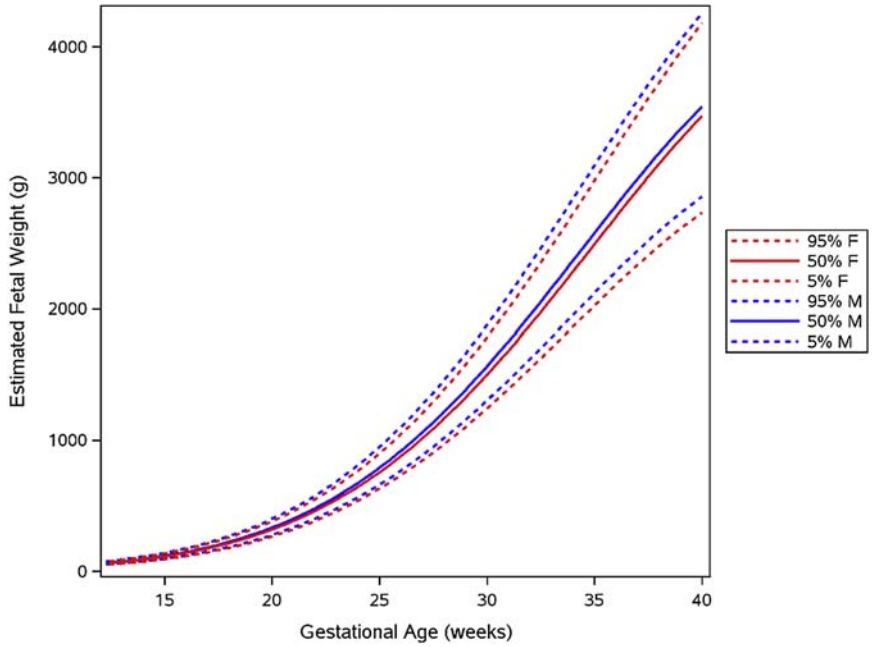


Fig. 2.9
Female and male growth of estimated fetal weight during gestational weeks 14–40 (5th, 50th and 95th centiles).

Customized fetal weight charts

A conceptually opposite approach to that of the single population growth standard is the concept of the customized growth chart. The most widely used of this type of chart are those developed by Gardosi et al.[52] and in the UK, the Royal College of Obstetricians and Gynecologists (RCOG) have recommended their use in clinical practice.[53] Specific to each fetus, these charts adjust for maternal characteristics known to have physiological effects on fetal growth.[54] These variables can then be used to calculate a "Term Optimal Weight" (TOW) for each individual neonate at the end of a normal scan-dated pregnancy (modal length of gestation assumed to be 280 days). In order to assess size in utero, the TOW is combined with a proportionality equation which links the EFW during gestation, to birth weight and in so doing, produces a "gestation-related optimal weight curve" (GROW).[55] This proportionality formula, however, is subject to various assumptions, namely that different fetuses will display a similar fetal growth pattern but at differing velocities to obtain their respective birth weight at term; that each maternal characteristic entered as a covariate affects the fetus in a constant manner throughout gestation and that the coefficient of determination (SD/weight), used to calculate the centiles, is also constant throughout gestation. As these assumptions have been questioned,[56–58] other approaches have been developed in order to produce individualized fetal weight charts.[58,59]

Modeling fetal growth

Despite routine care in the UK only including one ultrasound scan for the assessment of fetal growth (the "20 week scan"), it is nonetheless becoming increasingly common for women to obtain repeated measurements of fetal biometry across the course of gestation. With these serial measurements, it is possible to identify patterns of fetal *growth* and not simply fetal *size*.

A necessary first step when preparing to model fetal growth data is to perform data cleaning. Cleaning of fetal growth data should follow a similar approach to that applied to growth data observed in other periods, e.g. checking diagnostic plots of the marginal (e.g. histograms) and conditional distributions (e.g. scatter plots) in order to understand the distribution of the fetal biometric variable and thus identify any outliers. Another important data cleaning step which is more relevant when analyzing fetal growth data compared to other periods of the life course, is the identification of negative growth increments. It is expected that a fetus will increase in size between two measurements and thus it is important to identify cases in which size has decreased between two time points. If any cases are identified, it is necessary to determine which measurement(s) of the two, are erroneous. This decision can be facilitated by checking weekly average values for each of the two observations.

After identifying the distribution of the biometric variables from the above diagnostic plots, a transformation may be required. A commonly used transformation for fetal growth data is the natural logarithm,[37–44] as this is able to address the increasing variability in fetal biometry across gestation and produce a more constant variance. The natural logarithm is the number to which a base number, e(2.718 (3 d.p)), has to be raised in order to get the original number. For example, ln(3000) = 8.006 (3 d.p). To return to the original scale of measurement (e.g. grams or millimeters), the exponential (ex) of the value is taken and then the obtained value is referred to as the geometric value. The interpretation of the coefficients for a log-transformed dependent variable is that any independent variable is associated with a % change in the dependent variable.

After data cleaning and distributional assumptions have been checked, the next step is to develop the fetal growth model. The most common approach to modeling serial fetal biometry has been with multilevel models,[60] though other approaches are available (e.g. growth mixture model[61]). Multilevel models recognize the hierarchical nature of longitudinal data, dealing with the intercorrelation of serial measurements within an individual by classifying individuals as the level 2 units and measurement occasion as the level 1 units. Treating measurement occasions as nested within the individual "allows the investigator to proceed without difficulty when the number and spacing of the time points vary across cases".[62] For fetal growth data, this property is vital, as in a given sample of

pregnant women, few will have the same number/timing of measurements over the course of pregnancy. The exact specification of the fetal growth model will depend upon the data available as well as the research question being asked, but as with any growth model, the primary independent variable will be some function of age, or here, gestational age, in order to obtain a "growth curve" that best fits the data. To this end, fractional polynomials,[63] adapted from conventional polynomials, provide a flexible way of modeling growth curves and have been used widely in the modeling of fetal growth data[64–70] (see chapter on "Modeling growth curves for epidemiology" for a more detailed discussion on their use).

Factors affecting fetal growth

The placenta

The placenta is an interface between the mother and fetus and is therefore a critical organ involved in the regulation of fetal growth. A simplified illustration of the maternal-fetal exchange surface is shown in Fig. 2.10. The placenta must coordinate fetal cues and maternal signals to adequately match fetal demand and maternal substrate availability. For an overview of placental development, see Kliman.[71]

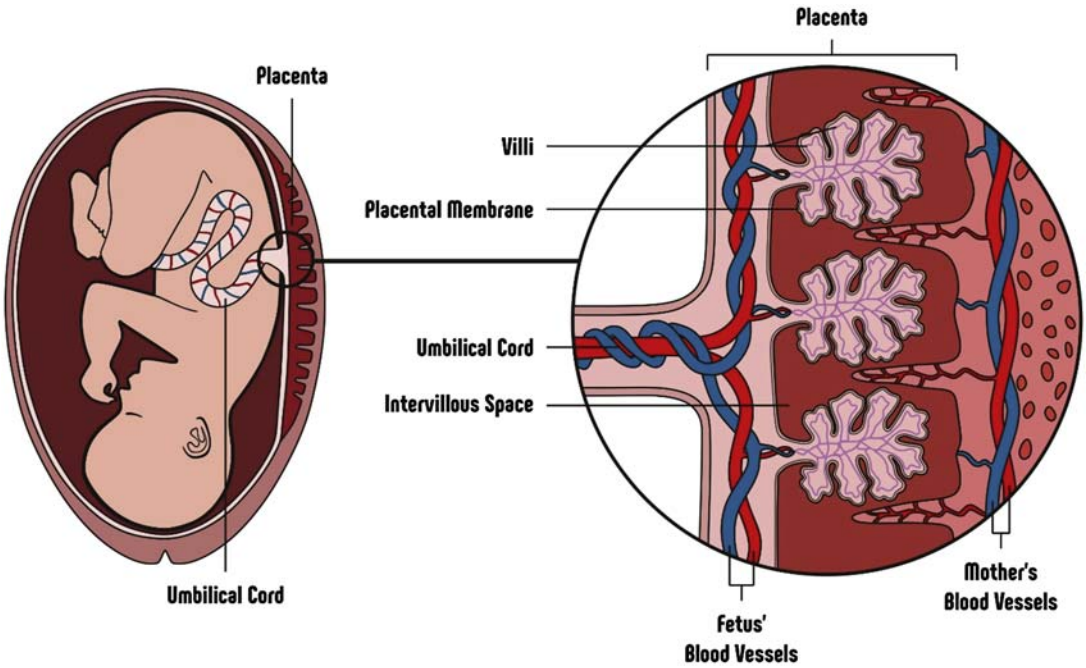


Fig. 2.10
The site of fetal-maternal exchange within the placenta.

The placenta has three general functions: (i) the transfer and metabolism of nutrients and waste products (ii) as an endocrine organ and (iii) protection[72,73] and the following sections will provide a brief overview of the first two.

Transfer and metabolism of nutrients and waste products

Transfer of nutrients and metabolites typically occurs via three methods; (i) simple diffusion, (ii) facilitated diffusion, (iii) active transport. Glucose is the principal carbohydrate substrate for both placenta and fetus[74] and must be obtained from the maternal circulation as the fetus is incapable of gluconeogenesis.[73] The transfer across the placenta is facilitated by glucose transporters, primarily, glucose transporter 1 (GLUT1)[75] and glucose transporter 3 (GLUT3).[76] Transport of amino acids is essential for protein synthesis and thus fetal growth.[77] As amino acids are more abundant in the fetal circulation (compared to the maternal),[78,79] active transport is needed to transport them across the placenta. This is achieved via amino acid transporters located in the microvillous and syncytiotrophoblast. Free fatty acids and glycerol can either travel across the placental membranes via simple diffusion, due to their lipophilic nature, or facilitated by fatty acid binding proteins in the membrane and cytosol.[80]

Endocrine organ

The placenta produces a number of steroid and protein hormones, some of which are unique to the placenta, making it an endocrine organ in its own right.[72] Hormones produced by the placenta include progesterone, estrogens, human chorionic gonadotropin (hCG), placental lactogen, placental growth hormone (PGH) and the growth factors IGF-I and IGF-II.[73,81]

Maternal size

Height

In the landmark meta-analysis of determinants of low birth weight, Kramer reported that each centimeter increase in maternal height was associated with a 7.8 g increase in birth weight, after adjusting for ethnicity, pre-pregnancy weight, age and socio-economic status.[54] This positive association between maternal height and birth weight has been widely replicated.[52,82–84] Furthermore, shorter maternal height has been associated with increased prevalence of SGA delivery and this association may persist over two generations.[85] While height and ethnicity have been observed to exert independent effects on birth weight, Leary et al. reported that adjusting for maternal height substantially reduced the geographical differences observed in birth weight, with a magnitude of up to 200 g in some studies.[83] A positive association also exists between maternal height and birth length, i.e. taller mothers give birth to longer infants.[84,86,87] The effect of maternal height on size and growth of fetal dimensions in utero has also been studied and appears

to have a stronger association with dimensions reflecting skeletal growth (HC, BPD, FL) compared to that of non-skeletal tissue (AC).[84,88,89]

Maternal height not only reflects the genetic potential for growth,[90] but also provides information regarding the environment experienced by the mother, i.e. her past and present nutritional status.[88] The nutritional status of the mother affects the energy available to the fetus and thus its own nutritional status. Maternal height therefore provides insight into both the genetic and environmental milieu experienced by the fetus. It is unsurprizing then, that maternal height is strongly associated with fetal and neonatal size and growth.

In an attempt to disentangle the causal mechanisms linking maternal height and fetal growth, Zhang et al. employed a Mendelian Randomization (MR) approach, in which known genetic variants (or "single nucleotide polymorphisms" (SNPs)) for maternal height were used as "instrumental variables" to test the causal effect of maternal height (phenotype) on offspring birth weight and length. They concluded that "the observed association between maternal height and fetal growth measures is mainly defined by fetal genetics", i.e. via the inheritance of height-raizing genetic variants.[91] However, another more recent MR study has suggested a greater role of the indirect effects of maternal height-raizing genetic variants (i.e. those not inherited by the fetus but which influence fetal environment, e.g. by increasing space available for growth).[92] Despite disagreement on the relative contribution of direct and indirect effects of maternal genetic variants, both of these studies confirm a causal effect of maternal genetic variants on birth weight, meaning the association is not simply a reflection of an improved maternal nutritional status.

Weight

Independent of height, a positive association has been reported between maternal pre-pregnancy weight (or body mass index (BMI)) and offspring birth weight.[54,86,90,93] Tanvig et al. report a significant positive association between pre-gestational BMI and birth weight, with each 1 kg/m^2 increase in maternal BMI resulting in an increase of 14.2 g. Furthermore, the study also revealed a significant positive association with birth AC, with each 1 kg/m^2 increase in maternal BMI resulting in an increase 0.5 mm.[94]

Looking directly at estimated fetal weight in utero, Ay et al. reported a positive association between maternal pre-pregnancy BMI quintile and EFW growth rate from mid gestation onwards [difference in grams per week compared to first quintile of 1.99 g, 1.74 g, 2.83 g and 4.39 g for the second, third, fourth and fifth quintile respectively.[86] Albouy-Llaty et al. also report an association between maternal pre-pregnancy BMI and fetal AC. When categorizing mothers as either under/normal/overweight or obese, they reported a positive trend between BMI classification and AC size between 20-25 weeks and 30−35 weeks. This trend became progressively stronger with gestation, so that at 30−35 weeks, the

difference between the fetuses of underweight and obese mothers was approximately equal to one week's growth in AC.[89] This pattern of an increasingly positive association between maternal weight and fetal dimensions as gestation progresses was also observed by Thame et al.[84]

Maternal weight is also influenced by both genetic (though to a lesser extent than maternal height) and environmental factors. As such, and as is the case for maternal height, the mechanism driving the positive association between maternal weight and fetal growth could be a result of the transmission of shared genetic variants which are associated with the regulation of fat and fat free mass. Alternatively, even in the absence of this expression, maternal weight reflects maternal nutritional stores, and thus potentially the nutritional reserves available to the fetus, therefore representing another mechanism via which maternal weight may contribute to fetal growth. In another MR study, Tyrrell et al. tested whether maternal BMI was causally associated with offspring birth weight and observed that a 4 kg/m^2 genetically higher maternal BMI (1 SD) was associated with a 55 g increase in birth weight.[95] However, unlike the study by Zhang et al., which suggested that the association between maternal height and fetal growth was unlikely to be driven by the intermediate effects on the intrauterine environment,[91] this study revealed that part of the association between maternal BMI and increased fetal growth may be partially mediated by the effect of higher BMI on circulating maternal fasting glucose.[95]

Parity

Parity refers to the number of times a woman has given birth to a fetus (alive or stillborn) with a gestational age of 24 weeks or more.

It has long been recognized that the first-born infant is smaller than subsequent offspring. For example, McBurney found that primiparous women (i.e. giving birth to their first child) were overrepresented in a group of mothers delivering intrauterine growth restricted (IUGR) offspring.[96] In the ALSPAC cohort (UK), Ong et al. reported a primiparous birth weight deficit ranging from 200 to 300 g depending on the extent of maternal parity (Para 1 vs. Para 2+). Infants of primiparous women were also significantly shorter, had smaller head circumferences and were thinner (lower ponderal index) compared to multiparous women (i.e. having already given birth to at least one child).[97] Gluckman & Hanson regard this first pregnancy effect as similar to that of smoking.[98] A systematic review evaluating the risks associated with nulliparity versus multiparity reported a significantly increased risk of SGA (OR 1.89, 95% CI 1.82, 1.96) and LBW (OR 1.41, 95% CI 1.26, 1.58) in nulliparous infants.[99]

The mechanism by which parity exerts this effect is not well understood. One proposed mechanism is via a more efficient physiological response in subsequent pregnancies,

particularly of the uteroplacental vasculature.[100,101] For example, it has been shown that the spiral arteries contained in the uteroplacental structure may be more able to fully dilate or be invaded by trophoblasts in subsequent pregnancies,[102,103] thus resulting in an increased delivery of nutrients in higher order pregnancies. Another possibility, however, is that parity is acting as a proxy for several maternal factors which are related to fetal growth and are known to vary over a woman's reproductive lifespan (e.g. weight, diabetes status). However, in attempting to unpick this, Hinkle et al. observed that maternal demographic, medical conditions, and weight-related changes that occurred between pregnancies did not explain the observed association between increasing parity and fetal growth.[104]

Maternal age

In England and Wales, the number of women giving birth at an older age is increasing. In 2018, 23% of all births were to women aged 35 or older, compared to 17% in 2000, an increase of around 35%. This increasing desire to delay parenthood has seen the average age of women giving birth increase from 28.5 years in the year 2000, to 30.6 years in 2018.[105]

A "U-shaped" relationship has been observed between maternal age and fetal growth, with both young and advanced maternal age conferring a greater risk of reduced fetal growth.[106–110] Lawlor et al. added robust support for these findings, observing, in a study of 642 979 primigravid Danish women, that outside of the lowest risk age category (25–29 years), the incidence of SGA rose with decreasing or increasing maternal age.[111] Findings concerning the effect of maternal age on ultrasonographically derived estimates of fetal biometry in various periods of gestation are equivocal,[58,112–115] but are suggestive of a greater effect in the final trimester.

Various theories have been proposed to explain the association between reduced growth and both young and advanced maternal age. For younger women, it has been suggested that there may be an increased competition for resources between the fetus and the still maturing gravida.[116,117] The increased risk observed with an advanced maternal age is speculated to operate via a declining functionality of the reproductive system,[118] which may ultimately lead to a less efficient placenta and thus impaired delivery of resources to the fetus. However, it has been argued that the confounding role played by socioeconomic position should be considered when investigating age effects on fetal growth. Specifically, younger pregnant women (particularly teenagers) are more likely to be of a lower SEP than older pregnant women and therefore subject to greater exposure to the various predictors of reduced fetal growth (e.g. poor diet, poor antenatal care) that are associated with a lower SEP, and vice versa for older women. Lawlor et al. provide support for this hypothesis in their sibling analysis of 264 695 women. They observed that after

controlling for SEP, the increased risk of SGA births seen in younger women was greatly attenuated while the association was strengthened at older ages, to the extent that the relationship between age and SGA-risk switched from a "U" shape association to one of increasing risk with advancing age.[111] However, contrary to the study by Lawlor et al., a more recent sibling analysis reported no association between advanced maternal age and SGA once SEP was accounted.[119] Further research is clearly needed to disentangle these associations.

Gestational diabetes

In the UK up to 5% of pregnancies involve women with diabetes. Of these, 87.5% are pregnancies in which gestational diabetes (GDM) develops.[120] Gestational diabetes is defined as insulin intolerance of any degree with onset or first recognition during gestation.[121,122] A degree of insulin resistance is a normal physiological response to pregnancy, due to the production of pregnancy hormones such as human placental growth hormone and human placental lactogen (HPL) and increased secretion of estrogen, progesterone, cortisol and prolactin[123]. This pregnancy adaptation leads to an increased level of glucose in the maternal circulation, resulting in a greater nutrient availability for the developing fetus. However, the increase in blood glucose requires a compensatory increase in the production of insulin to maintain a normal glucose tolerance and this achieved in approximately 97–98% of all pregnancies.[124] As gestation progresses into the third trimester, the challenge put on the pancreatic beta cells increases and in women whose insulin response is inadequate, GDM will develop. It is therefore at this time (24–28 weeks) that testing for gestational diabetes is routinely done.[125]

Gestational diabetes leads to accelerated fetal growth and increases the risk for delivering a baby classified as large-for- gestational-age (birth weight >90th centile) or macrosomic (birth weight >4000 g). A hypothesis attempting to explain this association was first proposed by Pedersen[126] and there are countless studies, notably the influential HAPO Study,[127] supporting it. The "Pedersen Hypothesis" states that the maternal hyperglycaemia observed in the presence of gestational diabetes leads to fetal hyperglycaemia and consequently an exaggerated fetal response to insulin, therefore resulting in greater fetal utilization of glucose.

Hypertensive disorders of pregnancy

The term "hypertensive disorders of pregnancy" is used to categorize a number of hypertensive disorders which affect pregnancy. Included are chronic conditions which either predate pregnancy or are diagnosed before 20 weeks gestation, e.g. hypertension, white coat hypertension and masked hypertension. In addition, the term also incorporates de novo hypertension, diagnosed after 20 weeks of gestation and includes gestational

hypertension and pre-eclampsia.[128] Together, these hypertensive disorders of pregnancy affect up to 10% of pregnancies, making them the most frequent pregnancy complication.

While gestational hypertension is not usually associated with abnormal fetal growth, approximately 25% of women with gestational hypertension will progress to preeclampsia,[129] which is a more serious medical disorder and a major contributor to maternal and fetal morbidity and mortality. Preeclampsia is diagnosed as the presence of de novo hypertension after 20 weeks gestation accompanied by proteinuria and/or maternal acute kidney injury, liver dysfunction, neurological features, hemolysis or thrombocytopenia, or fetal growth restriction. Given the criteria used to diagnose preeclampsia, it is unsurprizing that it is associated with substantial reductions in fetal growth and increased risk of SGA delivery.[130–132]

A direct cause of preeclampsia and the associated fetal growth restriction is an abnormal placentation and thus a dysfunctional placenta.[133] Specifically, the failure of the maternal uterine spiral arteries that supply the intervillous space to undergo the required vascular remodeling results in a reduced placental perfusion.[134] This results in a significantly reduced blood flow to the placenta and thus a decrease in the transfer of oxygen and nutrients to the fetus. As a result of the subsequent fetal hypoxemia, there is a reduction in fetal growth as an attempt to reduce the metabolic demands of the developing fetus.[135]

Socioeconomic position (SEP)

Socioeconomic position refers to the social and economic factors that influence what positions individuals or groups hold within the structure of a society.[136,137]

A positive association has been observed between SEP and birth weight[138,139] and these socioeconomic disparities in fetal growth have increased over time.[140–142] Few studies have investigated the association between SES and in utero estimates of fetal growth. Hansen et al. reported that compared to fetuses whose mothers lived in the highest SEP areas, FL was 0.09mm−0.12 mm smaller at mid-gestation (13−26 weeks). However, associations with SEP and HC, BPD or AC were not found.[143] Conde et al. also investigated the role of SEP on fetal size at mid-gestation (20−22 weeks) and reported positive associations with HC and AC.[144] As these studies only looked at the effect of SES during mid-gestation, it was not possible to investigate how the association changes over gestation. However, Silva et al. used serial fetal biometry data spanning the second and third trimesters in fetuses participating in the Generation R cohort, to investigate how the association between SEP and fetal weight, HC, AC and FL changed over gestation. They observed SEP disparities which were greatest for HC and which increased progressively over the course of gestation, resulting in differences in fetal weight which were evident from late pregnancy onwards.[145]

Kramer et al. aimed to identify mediators of the association between SEP and reduced fetal growth and concluded that leading mediators included cigarette smoking, low gestational weight gain and short maternal stature.[138] Beard et al. found that in addition to smoking, which mediated the association between SEP and birth weight by approximately 40%, inadequate antenatal care also mediated the association, though only by 5%.[140]

Smoking

Maternal smoking during pregnancy is recognized as the most significant modifiable risk factor for low birth weight and preterm birth in HICs.[54,146]

While annual estimates reveal a declining trend in the prevalence of smoking during pregnancy in many HICs, the proportion of women who are still smoking at the time of delivery remains high. In England for example, data for 2019 reveal that 1 in 10 women were still smoking during pregnancy, though substantial regional differences exist.[147] The most recent available data for the United States (US) reveal a lower prevalence of maternal smoking, with 1 in 14 women reporting smoking during pregnancy.[148]

Compared to infants born to non-smoking mothers, the birth weights of those born to smoking mothers have been shown to be anywhere between 160 g and 320 g lighter,[149–153] depending on the number of cigarettes smoked per day, with a dose-response relationship reported.[154–156] Despite this dose-response relationship, the negative effects of smoking are evident even at the lowest levels of maternal smoking.[157] Maternal smoking has also been associated with reduced birth length, upper and lower arm lengths, arm circumference and adiposity.[158–162] Fetal biometry studies have revealed smoking effects occurring as early as the first trimester. For example, van Uitert et al. observed that fetuses of gravidas who smoked $\geq$10 cigarettes at the time of conception were significantly shorter at 6 and 9 weeks than their peers from non-smoking gravidas.[163] Similar results were found in the study by Mook-Kanamori et al.[28] The detrimental effects of smoking on fetal growth have also been observed later in gestation, particularly for growth of the fetal head,[164–166] but also for other dimensions such as mean abdominal diameter[167] and limb dimensions.[165]

Carbon monoxide and nicotine have been hypothesized as the most likely components of tobacco smoke which cause this reduction in fetal growth.[54] Carbon monoxide has an affinity for hemoglobin which is 210 times greater than that of oxygen,[168] and it therefore has the potential to cause significant fetal hypoxia.[169] For example, Schell & Knutsen estimated that if a mother smokes 40 cigarettes per day there will be a 60% reduction in blood flow to the fetus.[156] In addition, nicotine stimulates adrenal production of epinephrine, norepinephrine and acetylcholine[170,171] which not only results in vasoconstriction of placental vessels and thus less uteroplacental perfusion,[172] but can also act directly on the fetus by increasing fetal blood pressure.[173]

Ethnicity and geography

Differences in fetal growth across different regions and ethnic groups are well established.[174] In HICs mean birth weight has increased and the prevalence of LBW has fallen over the last century, though these trends have stabilized recently.[175] In LMICs, while recent trends reveal greater reductions in the prevalence of LBW compared to HICs, the overall prevalence of LBW remains significantly greater in these regions. In 2015, of the 20 million livebirths which were LBW, 91% were born in LMICs.[175] There is variation in these rates across LMICs however, with a LBW rate of 32.3% in Southern Asia, compared to 16.4% in Sub-Saharan Africa. That such variation is apparent even across LMICs, which may be expected to share similar nutritional and environmental challenges, suggests that the etiology of ethnic differences in fetal growth is complex and is likely to include other factors such as maternal size; maternal behaviors and maternal morbidities. This is supported by findings from migrant studies, which reveal persisting ethnic differences in fetal growth even after migration to higher income countries. In the UK for example, there has been a lack of increase in birth weights in South Asian populations.[176–178] This phenomenon has also been observed in other countries and in other ethnic groups.[179]

Ethnic differences in fetal growth as measured by ultrasound have also been reported. For example, it has been shown that growth as early as the first trimester is influenced by ethnicity.[26] Other studies have revealed ethnic differences in the growth of the cerebellum,[180] head circumference,[68,181] abdomen,[68,181,182] femur,[181,183,184] humerus[184] and weight[68,181] from mid-gestation. In a multi-ethnic sample from the Netherlands, Drooger et al. found that after adjusting for maternal weight, height, age, parity and fetal sex, the differences in fetal weight between most ethnic groups were attenuated, but in some groups, up to two-thirds of the differences were unaccounted for.[185] This supports a complex etiology for the observed ethnic differences in fetal growth, and may include contributions from genetics, differing maternal behaviors, morbidities and other known and unknown environmental factors.

Nutrition

Before the development of the placenta, the developing embryo receives nutrients via secretions from the uterine glands which accumulate in the space between maternal and embryonic tissues.[186] After placentation has occurred, fetal nutrient supply is haemotrophic, i.e. via the exchange of nutrients between maternal and fetal circulations.[187]

Nutritional regulation of fetal growth is mediated by the regulation of fetal hormones.[188] The major hormonal regulators of fetal growth are insulin and the insulin-like growth factors (IGF-I & IGF-II).[189] Insulin's primarily role is to stimulate the release of

IGF-I.[189,190] IGF-II is important for regulating embryonic and early fetal growth,[191] whereas IGF-1 is more dominant in the second half of gestation.[192] These growth factors, particularly IGF-I,[193] are regulated by fetal nutrient supply.[194–196]

In terms of macronutrients, glucose crosses the placenta in the greatest quantities and is the major substrate for fetal oxidative metabolism[197] and is particularly important in regulating the IGF growth factors.[196] The accretion of amino acids into proteins is another important component of fetal growth.[198] Amino acids are also the precursors of numerous hormones and the substrates for the production of many substances, including DNA.[199] Unsurprisingly therefore, a reduced maternal intake of protein has been associated with fetal growth restriction.[200,201] However, it has also been demonstrated that a high maternal protein intake is associated with reduced fetal growth.[202] Lipid metabolism has also been speculated to contribute to variation in fetal growth, given the considerable deposition of fat in the final trimester and the substantial contribution of neonatal adiposity to birth weight. While the transfer of lipids across the placenta is difficult,[203] the pregnancy-related changes in maternal lipid metabolism (e.g. accumulation of fat stores and hyperlipidemia) are thought to contribute to fetal growth, with studies observing that maternal plasma triacylglycerols (TAG) and non-esterified fatty acids (NEFA) correlate positively with cord blood lipids and fetal growth.[204–206]

Micronutrients play a vital role in embryonic and fetal development, particularly in early gestation (e.g. folate). In the UK for example, it is recommended that women attempting to get pregnant and those in the first 12 weeks of gestation should take a daily supplement of 400 μg of folic acid and a 10 μg supplement of vitamin D.[8] However in a review of the literature, Fall et al. concluded that there was no good evidence to suggest that supplementation of single micronutrients during gestation improves fetal growth. Supplementation with multiple micronutrients in undernourished women from low income countries has however, provided more favorable results.[207,208]

In summary, fetal growth is the product of a range of maternal, genetic, fetal and placental factors. Maternal height and weight are both strongly implicated in the regulation of fetal growth, whether this be via transmission of shared genetic variants to the fetus or their impact on the in utero environment. Global variation in fetal growth has been observed and likely reflects contributions from genetics, differing maternal behaviors and morbidities, as well as other known and unknown environmental factors. The placenta, acting as the interface between the mother and fetus, is a crucial organ involved in the exchange of nutrients (including glucose and various amino acids), respiratory gases and waste products. A well-functioning placenta is therefore critical for optimal fetal growth. A sub-optimal placental development can lead to serious complications, including preeclampsia, which is a major disorder of pregnancy associated with significantly reduced fetal growth. Another disorder of pregnancy associated with altered fetal growth and

warranting mention because of its increasing incidence is gestational diabetes. Unlike preeclampsia however, this condition is typically associated with substantial increases in fetal growth.

Birth

Transition from utero to postnatal environment

The process of birth represents a critical transition for the infant, during which it leaves the relatively stable environment experienced in utero and moves into the more volatile postnatal environment. For example, in addition to having to adapt to changes in external temperature, sensory stimulation and oxygen supply, the infant has to transition from an environment in which nutrients were received in a relatively stable and chronic manner to one in which the supply of nutrients is more variable and reliant upon external sources, especially after the end of exclusive breastfeeding. The difficulty in making this transition is evidenced by the rate of deaths occurring in the first few weeks of birth, with neonatal deaths (deaths within the first 28 days since birth) accounting for almost half of all deaths in infants and children younger than 5 years.[209] A significant proportion of these neonatal deaths are attributable to sub-optimal growth in fetal life, be it too much or, more commonly, too little growth. Some of the measurements recorded at birth and used to identify increased or reduced fetal growth, are described below.

Measurements taken at birth

In many settings, particularly in LMICs,[210] it may not be possible to obtain estimates of ultrasonographically-derived fetal biometry in order to assess the adequacy of growth in utero. In such settings, an assessment on the adequacy of fetal growth can only be made at birth with various cross-sectional measurements of new-born size, typically (though not universally) weight, length and head circumference. In the UK for example, routine assessment at birth includes measurement of only new-born weight and head circumference.[211] Indeed, the most common definitions used in both clinical and research settings to indicate inadequate growth are all based on new-born weight. These are: low birth weight (LBW) and small-for-gestational age (SGA), together representing reduced fetal growth and conversely, macrosomia and large-for-gestational age (LGA), representing increased fetal growth.

- Low birth weight (LBW): birth weight <2500 g irrespective of gestational age at birth
- Small-for-gestational-age (SGA): birth weight <10th centile (5th/3rd are also used) for a given gestational age
- Macrosomia: birth weight >4000 g irrespective of gestational age at birth
- Large-for-gestational age (LGA): birth weight >90th centile (95th/97th also used) for a given gestational age.

Caution should be warranted when using these cross-sectional measurements to evaluate fetal growth, as by definition, an assessment of growth requires serial data. This issue is illustrated in Fig. 2.11, in which three infants are measured at birth along with their (unobserved) in utero growth curves. At birth, curve "A" represents an infant who is classified as appropriate-for-gestational age (AGA) at birth but had serial ultrasound measurements been available in utero, may have been identified as demonstrating restricted fetal growth. Conversely, curve "C" depicts an infant who is classified as SGA at birth, but who appears to have demonstrated a stable pattern of growth throughout pregnancy, tracking along the same, albeit low, weight centile. Finally, curve "B" is an infant who was classified as SGA at birth and who also appears to have exhibited restricted growth in utero. Taken together, these scenarios exemplify the potential to misclassify the adequacy of fetal growth based on a single measurement taken at the end of the intrauterine period. As mentioned previously however, in many settings serial fetal biometry data are not available and thus classifications of SGA and LGA represent an easily obtainable proxy. Furthermore, classifications of SGA and LGA have prognostic importance, both being associated with a range of short- and long-term adverse outcomes.[212,213]

Growth charts used at birth (UK)

In order to obtain these classifications of SGA and LGA, birth weight has to be plotted onto a chart. In 2009, the UK-WHO growth standard for children ages 0–4 years replaced the previously used UK90 references [214]. The WHO standard was based on term-born

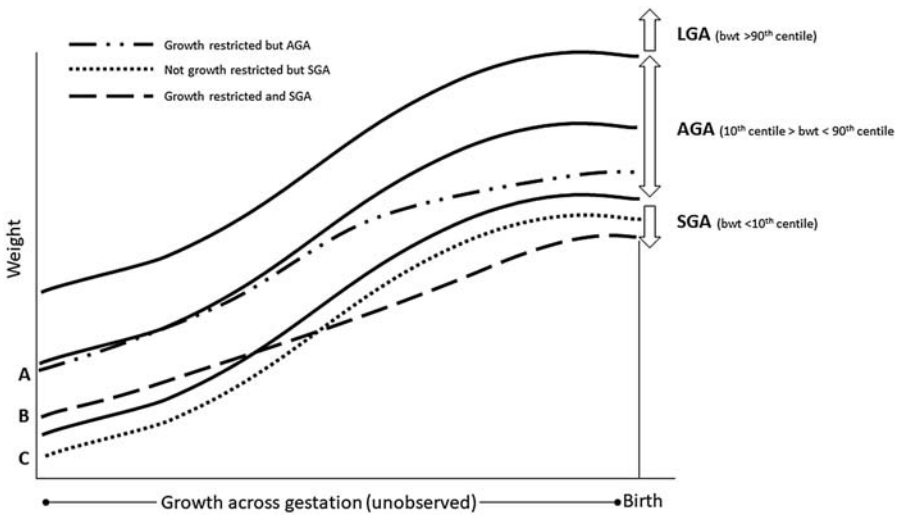


Fig. 2.11
The potential for misclassification when using size at birth as a measure of fetal growth.

children, to non-smoking mothers whose socio-economic environment would not constrain their growth.[215] These children came from six different countries and thus the charts represent global standards. In the UK however, it was necessary to retain the former charts, the UK90 references, for assessment at birth, as not only did the UK-WHO charts have no preterm section (by design), but also because the WHO mean birth weight for term births was significantly lower than in the UK.[216] The UK90 references however, were constructed using a sample of White British infants only, as it was thought that there may be differences in growth in "ethnic non-white children".[217] Recently a new set of birth weight charts have been produced for the UK,[218] based on over 1.2 million births across all ethnic groups, occurring in England and Wales in 2013−14. These references are a more contemporary and representative tool with which to evaluate birth weight, taking into account the medical, social and legal changes which have occurred since the UK90 charts were developed, and also the changes in the ethnic composition of the population. While ethnic groups were pooled in these updated charts, the authors acknowledged the existence of ethnic variation in birth weights. It has been shown for example, that UK born South Asians are 200 g−300 g lighter at birth compared to White British infants.[219,220] Accordingly, birth weight charts for some ethnic minority groups in the UK,[221,222] and in other countries,[223,224] have been produced. These charts allow a more personalized assessment of size at birth, helping to determine whether an infant is small or large as a result of a pathological growth perturbation and therefore at risk of neonatal morbidity/mortality, or whether the infant is constitutionally small or large and therefore healthy. Indeed, using the conventional cut-offs to identify SGA (<10th centile) and LGA (>90th centile), ethnic specific charts have been shown to perform significantly better than population references at identifying infants at higher risk of neonatal morbidity and mortality.[225−227]

Just as customized fetal weight charts have been developed for the intrauterine period, customized birth weight charts have also been developed[52] and are recommended by the Royal College of Obstetricians and Gynecologists.[53] However, the evidence is inconsistent with regard to their clinical utility.[222,228−231]

Infant growth

Pattern of infant growth

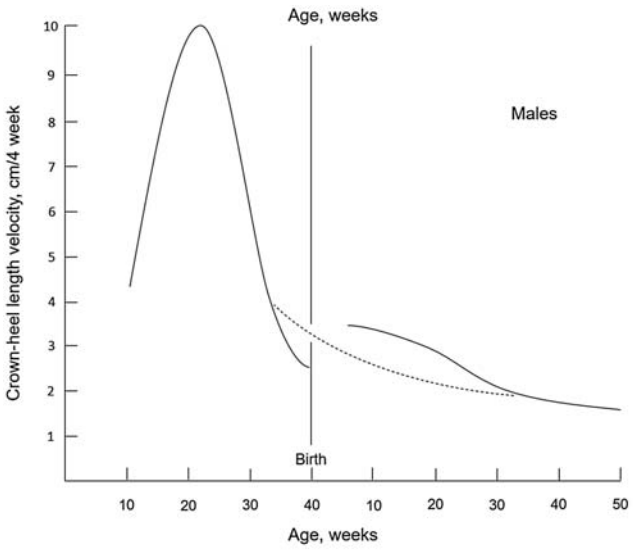
Infancy refers to the first two or three years of postnatal life.[232] It is the postnatal period associated with the most rapid growth velocity, however it is common for babies to lose up to 7% of birth weight in the first few days,[233,234] but which is mostly regained by the 14th day. During the first year of life, the average infant will grow at a rate of 25 cm/year,[235] with an average velocity of around 18 cm/year for the entirety of infancy. Weight velocity is also high, with a typical infant adding up to 7 kg in the first year. With average

birth weight approximately 3.5 kg, the addition of a further 7 kg represents a 200% increase in weight in the first year. Despite exhibiting the greatest velocities in weight and length growth over the life course, infancy is also marked by a rapid deceleration in these velocities,[235] as is shown in Fig. 2.12. The characteristic declining velocity of infancy is a continuation of the trajectory observed in utero, in which the rate of growth, at least for length, is at its maximum in the second trimester and decreases thereafter until childhood.

Features of infant growth

Maternal size versus genetics

As discussed earlier, maternal size and the intrauterine environment play an important role in regulating fetal growth and thus size at birth. In a classic experiment demonstrating the role of maternal size on the size at birth, Walton and Hammond crossed a Shire horse mare with a Shetland pony stallion, and vice versa.[236] Despite offspring sharing the same proportion of genes from each parent, the foal of the Shire horse mare was considerably larger at birth than the foal born to the Shetland pony mare. Thus, maternal regulation was the predominant factor in determining the growth rate in utero. The same has also been demonstrated in humans, with Tanner reporting a correlation of 0.2 between size at birth and adult size, but which rises sharply during infancy to result in a correlation of 0.8 at two years.[237] More recent studies have, however, highlighted a greater contribution of



Adapted from 'Foetus into Man' Tanner (1990) (2nd edition)

Fig. 2.12
Growth velocity (length) in the pre- and postnatal periods.

genetics (fetal or maternal) to size at birth.[91,92] An accurate estimate remains largely unknown, with heritability estimates ranging from anywhere between 25 and 67%.[238–241] While the precise impact of genetics on size at birth is less clear, it is well known that genetics plays a greater role in the regulation of size and growth during infancy.[241–244] That genetics becomes the more influential regulator of growth only after birth is an adaptive mechanism that allows a genetically large fetus (i.e. with large parent(s)) to be born to a small mother.

Catch-up growth and canalization (types of catch-up growth)

An inevitable consequence of this relationship is that during infancy a large proportion of infants shift centiles upward or downward in order to express their genetic potential. Indeed, Smith et al. observed that about two-thirds of infants shifted percentiles in the first two years of life: one-third being genetically large infants whose growth was constrained in utero and thus exhibiting "catch-up" growth, and one-third being genetically small infants who experienced favorable prenatal conditions and thus demonstrating "catch-down" growth.[245] The term "catch-up growth" was originally defined by Prader et al. as the increase in growth after the removal of a factor that had previously constrained it.[246] The original context in which it was applied was with regard to growth inhibiting illnesses such as growth hormone deficiency, hypothyroidism and Cushing syndrome, however it has since been used to refer to the growth acceleration seen in those who experienced growth constraint in utero.

Types of catch-up growth

Since the original definition, several forms of catch-up growth have been documented that serve to resolve growth inhibition and potentially lead to the same normal adult height. Tanner distinguished three patterns of catch-up growth and labeled them A, B and C.[247,248] Type A is generally regarded as the classic form of catch up growth and is common in infancy. In this form of catch-up growth, when the growth inhibition is removed, velocity increases rapidly to quickly eliminate the growth deficit and return the individual to their previous growth curve, after which velocity returns to normal. In type B, once the restriction is removed, growth velocity increases only by a small amount. Instead, the deficit is compensated for by a total growth period which is longer than usual. This type of catch-up growth has been observed in several LMIC settings, including the Gambia.[249] In type C, the growth velocity does not show any increase above the average for chronological age but as bone maturation is delayed, growth continues for a longer period. However, as was acknowledged by Tanner, type C cannot formally be considered catch-up growth as there is no increase in velocity after the growth inhibition has been removed. More recently, another type of catch-up growth has been proposed, type AB.[250] This is characterized by an initial period of faster than normal growth for bone age, which then

passes into a phase of stable height centile tracking, though remaining below the target height centile, until a delayed puberty causes a further increase in height toward the target height centile.

Canalization

An underlying assumption of catch-up growth is that individuals have a predetermined growth trajectory that they should follow over the period of growth. C.H Waddington was the first to describe this phenomenon, coining the term "homeorhesis" or "canalization" to describe the in-built regulation of developmental pathways to return to a particular trajectory after genetic or environmental interference.[251] This is a pre-requisite for catch-up growth, i.e. if an individual does not have this predisposition to adhere to a particular centile or "canal", it would not be possible to identify instances of catch-up growth.

The outcomes of catch-up growth: unpicking the inconsistencies

Historically, catch-up growth has been based on linear growth and deemed a normal response to fetal constraint. Its usage today has changed however, particularly in high income countries (HICs). In these settings, where the burden of undernutrition is less and there is an increasing burden of overweight and obesity, the focus has shifted to the epidemiology "catch-up in weight" or "rapid infant weight gain". Therein lies one of the confusions in the literature: these two distinct terms are used synonymously. In their highly cited paper looking at catch-up growth and childhood obesity, Ong et al. defined catch-up growth simply as a "a gain in SD score for weight between zero and two years that was greater than 0.67 SD score".[252] This definition however, fails to distinguish between those who demonstrate increased growth as part of a compensatory response to prenatal growth constraint, and those demonstrating upward centile crossing as a result of excess energy intake. Since this landmark paper, unsurprisingly numerous studies have demonstrated an association between "catch-up" in weight and an adverse cardiometabolic profile in later life.[253–255] Whether these infants are indeed displaying catch-up growth or just rapid infant weight gain is not known. This distinction is needed as if infant weight gain is a compensatory response to fetal growth constraint, it would not be expected to be associated with adverse outcomes. A handful of studies have attempted to shed light on this issue by investigating whether the effects of infant weight gain differ by the pattern of fetal growth (e.g. restricted or rapid) as measured by ultrasonography.[256–259] These studies observed a general pattern that any rapid infant weight gain was associated with adverse long-term cardiometabolic outcomes, in line with the growth acceleration hypothesis,[260] but that the associations differed depending on the outcome investigated.

Conversely, in LMICs, where growth restriction experienced in utero is common and leads to high rates of childhood stunting (height-for-age$<$2 SD scores), the original definition

of catch-up growth typically predominates. In these LMICs, catch-up growth has been shown to provide some protection against the high incidence of infections in early life[261] and thus reduce infant mortality and morbidity.[262,263]

The positive findings observed in LMICs paired with the long-term negative outcomes observed in HICs has led to the notion of a "catch-up dilemma".[264,265] However, to conflate the long-term consequences of catch-up in weight (or more likely- "rapid infant weight gain") in HICs and the benefits of catch-up in length in LMICs is inappropriate. As was shown by Adair et al., a clear distinction between linear growth and weight gain needs to be made. In their cross-cohort analyses of five LMICs, they observed that increased linear growth during the first 2 years of life was associated with gains in height and schooling (key aspects of human capital), with no or negligible adverse trade-offs in terms of chronic disease risk factors. This was in contrast to gains in weight, which had little benefit to human capital.[266]

Infancy as a nutrition dependent phase of growth

Infancy is sometimes referred to as the nutrition-dependent phase of growth because nutrition is the main factor influencing it. The recommendations from the WHO are that breastfeeding should be initiated within 1 h of birth and that infants should be exclusively breastfed until six months. Thereafter, to meet the evolving nutritional requirements of the infant, nutritionally adequate and safe complementary foods should be introduced while breastfeeding continues up to two years of age or beyond.[267]

For various reasons, exclusive breastfeeding is not always possible, in which case formula milk is provided. It is well known that differences in growth are apparent between breastfed and formula fed infants. During the first two or three months of life, findings are mixed regarding the difference in growth (gain in weight and length) between breast- and formula-fed infants.[268,269] However, from around two months of age to the end of the first year, a recurrent pattern has been observed, with formula-fed infants gaining weight and length more rapidly than breast-fed infants, such that by 12 months of age, formula fed infants weigh, on average, 400−600 g more than breastfed infants[268,270] and this difference persists until around two years.

From around 6 months onwards, breastmilk is not able to provide adequate amounts of energy and micronutrients needed to sustain growth. The initiation of complementary feeding is therefore advised at this time and this represents a change in the supply of nutrients received by the infant. If this complementary feeding is inadequate or insufficient, growth faltering between six and 12 months can occur, and this is a common phenomenon observed in infants at this age.[235] As such, the WHO recommend that complementary feeding should be timely, in that all infants should start receiving foods in

addition to breastmilk from 6 months; adequate, meaning the nutritional value of the foods should fulfill the needs of the infant; and appropriate, meaning complementary foods should be diverse and supplied in adequate quantity.[271] Furthermore, a set of eight infant and young children (IYCF) indicators have been established to assess the adequacy of infant and young child feeding practices.[272]

Indicators of infant malnutrition

A set of key anthropometric indicators exist which, while not able to be used to assess growth per se, are able to reveal the short- and long-term nutritional status of the infant. These were proposed by Waterlow et al.[273] and include:

Stunting

Stunting refers to those with low height-for-age and is a marker of chronic undernutrition, typically resulting from long-term exposure to poor diets or repeated infections. It is defined as height-for-age more than two standard deviations below the WHO Child Growth standards median.

Wasting

Wasting refers to low weight-for-height and is a result of acute undernutrition, as a result of insufficient food intake or a high incidence of infectious diseases (e.g. diarrhea). It is defined as weight for height more than two standard deviations below the WHO Child Growth Standards median.

Underweight

Underweight refers to a low weight-for-age. As this only requires the measurement of weight, it is the most commonly collected indicator. It is defined as weight for age more than two standard deviations below the WHO Child Growth Standards median.

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Suggested readings

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Internet resources

Intergrowth 21st − The International Fetal and Newborn Growth Consortium for the 21st Century. https://intergrowth21.tghn.org/.
Home of the Intergrowth 21st study, containing various standards, calculators and apps for quantifying fetal and infant growth, pregnancy dating, gestational weight gain and much more, as well as all of the publications from the study.
World Health Organization. Fetal Growth Calculator. http://srhr.org/fetalgrowthcalculator/#/.

Calculator for assessing fetal growth relative to the WHO fetal growth charts.

Gestion Network. https://www.gestation.net/.

Access to customized fetal growth charts and birth weight centile calculators. Also has software for calculating gestational age and fetal weight.

World Health Organization. The World Health Organization's Infant Feeding Recommendation. https://www.who.int/nutrition/topics/infantfeeding_recommendation/en/.

Includes links to WHO infant feeding guidelines and recommendations.

CHAPTER 3

Child and juvenile growth

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Introduction

As familiarly depicted, the human growth curve is characterized by a high rate of prenatal growth, a rapid deceleration in growth rate over the first two years postnatally, a relatively constant slow rate of growth until puberty, and an increased growth rate at puberty leading to the attainment of adult height.[122] Although this curve varies by sex, with girls showing an earlier and less marked increase in growth velocity at puberty, by individual, with the age of peak height velocity in pubertal boys ranging from 12 to 16 years, and by system, with skinfold thickness velocity, for example, increasing until 9 months of age, decreasing through early childhood and slowly increasing again after age 6–8, it has generally been used by human biologists and auxologists to represent the species-wide pattern of human growth.[15,59] Mathematical modeling of this curve requires at least three separate functions,[15,52,122] suggesting that these three segments of curve represent distinct phases of growth. As the need for three functions to define the human growth curve varies from both other mammals and non-human primates, the human growth curve has been theorized to represent not only a species-wide growth pattern, but also a uniquely human pattern that includes infant, childhood, juvenile and adolescent phases of growth.[15]

Within biological anthropology, childhood, usually defined as the period from weaning to the eruption of the first permanent molar and cessation of brain growth in weight,[15] roughly ages 2–6, has received considerable attention as the period that may be uniquely human. Compared to non-human primates and social mammals, human children have a slow period of physical growth after infancy during which they are still dependent on others for their care and feeding. This lengthier period of dependency has been hypothesized to permit greater investment in brain growth,[59,144] accumulation of metabolic and cognitive capital and increased survival during childhood and adulthood.[51] Whether this period is unique to humans or just prolonged in comparison to non-human primates, however, remains a source of debate. Recent longitudinal assessments of nonhuman primate growth and endocrinological development suggests that nonhuman primates may also have a period of childhood, albeit one that is more compressed than that of humans.[10]

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Whether this period is unique in kind or just duration, childhood is characterized by a unique set of needs compared to other points in the life course, due to the cognitive immaturity of children, their requirements for energy rich foods to fuel brain growth, and their immature dentition and digestive systems which limit the types and/or amounts of foods they can consume.[15] Recent estimates of the energetics of brain growth during childhood reveal that the magnitude of glucose uptake is highest in childhood both in absolute amounts and relative to the total metabolic budget.[144] Work by Kuzawa et al.[144] indicates that glucose use by the brain accounts for 66% of resting metabolic rate and approximately 43% of total energy expenditure in childhood. Perhaps unsurprisingly, this energy expensive brain growth is inversely associated with childhood physical growth rates in their study, supporting the hypothesis that the slow rate of growth during childhood represents an energetic trade-off to promote brain development.

Following childhood, the juvenile period, also known as middle childhood (approximately ages 7−11), begins with the eruption of the first permanent molar and ends with the pubertal growth spurt. Like childhood, the juvenile period is a time of slow growth. Unlike children, however, juveniles are more able to care for themselves. This period is an important one for cognitive development and social learning. A global reorganization of cognitive function occurs during this time, called the five-to seven shift, with concomitant improvements in perceptual abilities, fine motor control, and reasoning.[136] Along with this cognitive development, the period is marked by changes in body composition and the widening of sex differences in body composition. While sex differences in body fat are already seen in infancy, with girls having higher percent body fat, the greater deposition of lean body mass in boys compared to girls means that children enter puberty with considerable sex differences in body composition.[138]

Perhaps due to the slow and steady pace of growth, childhood and juvenile growth and development have received considerably less attention from health researchers than the first 1000 days of life (conception to age 2) in recent years. Nevertheless, the periods of early (ages 2−6) and middle (7−11) childhood may be important for shaping long-term health and function. These periods are characterized by changing body proportionality and composition, rapid brain growth and maturation, and hormonal development. Environmental factors shaping growth, particularly the rate of linear growth and adiposity gain, during this period may have long term impacts on cardiometabolic health, cancer risk and cognitive function. This chapter reviews the main characteristics of childhood and juvenile growth, describes factors contributing to variation in growth during childhood, discusses current health challenges for children, and concludes with a discussion of why childhood may be an important period shaping long term health.

Characterizing physical growth during childhood

Linear growth

The rate of linear growth slows from infancy into early childhood reaching a relatively constant rate of 6 cm/year in stature by 4–5 years of age with few differences seen between boys and girls.[98] Growth in stature remains steady during middle childhood, at approximately 5 cm/year from ages 7 to11. Sex differences in height develop during this period. Boys are 2 cm taller on average than girls at age 7, but girls are 1 cm taller by age 10 due to a faster rate of growth leading into puberty. Body proportionality also changes considerably during this period. During early childhood, the torso grows in relation to the head distinguishing the body proportionality of children from that of infants and toddlers. Growth during middle childhood tends to be faster in the legs than the trunk, leading to a more adult-like body proportionality.[108]

Mid childhood growth spurt

One of the key features separating the early and middle childhood (or childhood and juvenile) periods is the mid-childhood growth spurt. This mid-childhood growth spurt, which occurs between the ages of 4 and 8, is characterized by a slight increase in height velocity of 0.5 cm/year in boys and 0.3 cm/year in girls. However, the mid-childhood growth spurt has not been consistently seen across studies perhaps due to the dearth of longitudinal growth studies of preschool and school-aged children with frequent assessment. Identifying this slight increase in growth rate requires longitudinal growth monitoring during childhood with measurements occurring at least yearly across this period. Results from longitudinal and cross-sectional studies with sufficient sample sizes to estimate annual growth velocities have been mixed, with some studies finding evidence of the MCGS in boys but not girls [9,123] and others finding a spurt only in a limited proportion of children.[71] More recent studies using mixed models and Bayesian estimation have also found variable evidence of a mid-childhood spurt.[16,23,127] Towne and colleagues[127] found evidence of a mid-childhood spurt in just over half of 579 participants of the Fels Longitudinal Study. Marked sex differences were seen both in the presence of the spurt (79% of boys compared to 36% of girls) and its timing (4.8–6.3 years of age in boys and 3.9–4.8 in girls[127]). Sex differences in the timing of the mid-childhood spurt were also shown in a cohort of Korean children, where a mid-childhood spurt was documented at age 8 in girls and 10 in boys, a considerably older age than other samples, but still two years before pubertal peak height velocity.[23] In these studies and others, the magnitude of the spurt was quite small, leading some to question its clinical relevance.[98]

Body composition

Similar to height velocity, body mass index (BMI) declines from its peak in infancy through early childhood, reaching a nadir around ages 5–6. Unlike height velocity, however, BMI increases from this nadir across later childhood into adolescence. Termed the adiposity rebound (AR), this increase in BMI is linked to increased weight gain, not increased linear growth, and parallels changes seen in skinfold thickness.[101,122] The timing of the AR is quite variable between individuals and is associated with a number of factors including child sex, birth weight, genetic inheritance, diet, and other early life factors contributing to weight gain.[20,139] Girls, for example, tend to have an earlier AR peak than boys, and some evidence suggests that, in the United States, non-Hispanic black children have an earlier AR than their white peers.[139] The timing of AR is associated with development of overweight and obesity in adolescence and adulthood (discussed in more detail in section Child obesity, adiposity rebound and long-term outcomes), with earlier AR linked to the development of greater adiposity in subsequent years.

Whether increasing BMI during later childhood is due to increasing body fat, however, has been extensively questioned. Some research suggests that the majority of weight gain seen during this period, from 2 kg/year at ages 4–5 to 4 kg/year by age 10, is due to increases in fat free mass, particularly during the period of BMI decline.[138] However, more sophisticated methods for measuring composition, such as computed tomography (CT) and dual-energy X-ray absorptiometry (DXA) scans, show changes in both fat and fat free mass during later childhood.[143] Analysis of CT scans collected during the period of adiposity rebound in American children showed that total body fat (TBF) increased by 2.0 ± 0.9 kg/year between the ages of 8 and 13. This increase remained significant when controlling for total lean tissue mass, suggesting that TBF accumulated faster than lean body mass during this time period.[49] Similarly, among 6- and 11-year old children participating in the 2004 Pelotas Birth Cohort in Brazil, both fat and fat free mass indices, measured by DXA, increased across later childhood and the gain in fat mass was higher than that of fat free mass for both boys and girls.[107]

Sex differences in body composition

Along with shifting body composition, sex differences in body composition, already seen in percent body fat during infancy, become more pronounced during this period as the sexes differ in both their deposition of lean versus fat mass and the regional distribution of fat mass. Boys tend to develop more muscle mass in childhood than girls. For example, in a study of children aged 5–10 years old, boys had a 10% greater muscle mass than girls when matched by age, weight and height.[4] Conversely, in the Pelotas study, fat mass was already larger in girls by age 6 and continued to increase across the study period.[107]

Other studies similarly show that fat mass tends to increase across childhood in girls, while gains in TBF are less consistent in boys and are inversely related to increases in fat free mass.[39] As a result, girls end childhood with higher fat mass and body fat than boys, differences that are only accentuated during adolescence.[115]

While sex differences in body composition during childhood are well established, the emergence of sex differences in regional body fat patterning are less consistent. A number of studies have compared peripheral to central adiposity in children, with conflicting results likely due to differences in measuring technique (skinfolds vs. direct assessment) and inconsistent adjustment for overall body fat or body fat in other components.[124] Nevertheless, sexual dimorphism appears to exist in peripheral and central fat between boys and girls in middle to later childhood, though the exact timing of the emergence of these differences may vary across samples. Skinfold measures show that the absolute thickness of subcutaneous fat is higher in girls from at least 8 years of age onward.[137] Conversely, central adiposity tends to be higher in boys as young as 5−7 years old, when assessed through waist circumference.[137] Other studies using direct assessment have questioned whether differences in visceral adipose tissue exist prior to puberty. Some studies have found that girls have more subcutaneous abdominal fat throughout childhood compared to boys, who have more visceral adipose tissue.[111,115] However, others have found no differences.[49,58] In a large study of children and adolescents, differences in visceral adiposity did not appear until later in childhood/early adolescence.[115] Together, this research suggests that sex differences in overall body composition, fat vs. fat free mass, develop in childhood but that sex-specific patterns of adiposity (i.e. gynoid vs. android) may not become established until puberty with the increasing production of sex steroids.

Physiology of childhood growth

Unlike infancy, where nutrition is seen as a major determinant of growth, growth during childhood is thought to be more influenced by hormonal regulation.[8,52] Underlying the linear growth and body composition changes seen in childhood are a network of hormones that interact to control growth in length, adiposity and lean body mass in response to genetic inheritance, environmental exposures, and energy availability. Among these hormones, growth hormone (GH), insulin-like growth factor 1 (IGF-1) and thyroid hormone (TH) are particularly important in shaping growth trajectories during this period.

Growth hormones

GH stimulates long bone growth in children both directly at the growth plate and indirectly by stimulating the release of other trophic hormones, such as IGF-I. At the

growth plate, GH directly promotes cellular division and maturation. Systemically, GH activates liver cells to produce IGF-I, which then exerts direct effects on bone and other tissues. IGF-1 stimulates clonal expansion of chondrocytes, triggering linear growth, and plays a role in soft tissue growth, acting with GH and independently to regulate carbohydrate, fat, and protein metabolism.[46] These endocrine effects of IGF-1 are regulated by binding proteins, most commonly IGFBP-1 and IGFP-3, which transport IGF-1 to target tissues. These binding proteins are in turn regulated by insulin levels, potentially moderating the likelihood or rate of growth in response to energy availability.[8]

Both the amplitude and rate of growth are shaped by the production of GH.[8] The amount of GH produced is regulated by two factors: growth hormone releasing hormone (GHRH), which promotes the production of GH, and somatostatin (also called growth hormone inhibiting hormone), which suppresses GH. This dual regulation results in a pulsatile pattern of production as GH is turned on and off during the day.[102] The amplitude of GH pulses is associated with the amount of growth seen during any episode of growth and the frequency of pulses underlies growth rate.[102] The release of GHRH or GHIH are stimulated by many different factors such as blood glucose levels, available amino acids, stress, and exercise, meaning that a large number of environmental factors have the potential to shape GH production and, by extension, growth. GH, for example, is stimulated by ghrelin, a metabolic hormone produced by the stomach, and inhibited in a negative feedback loop with IGF-I,[8] allowing energetic signals to influence the production of GH. Sex differences in GH pulsatility may also underlie some of the sex differences seen in childhood growth. While sex differences in the release GH become more pronounced during puberty under the influence of sex steroids, sex differences are seen throughout postnatal development, with boys having larger, less frequent, and more orderly pulses of GH than girls, who have less regular pulses and higher tonic levels of GH.[99]

Thyroid hormones

Along with GH and IGF-I, thyroid hormones play an important role in childhood growth. Thyroid hormone receptors are seen in both the resting and proliferative zones of the growth plate, where they regulate chrondrocyte maturation, cartilage matrix synthesis and mineralization.[8] Thyroid disorders are associated with skeletal maturation and growth rate in childhood. Children with hypothyroidism experience delays in skeletal maturation and growth faltering. Conversely, hyperthyroidism advances skeletal maturation and is associated with growth acceleration, early closure of the growth plates and shorter final height.[142] These growth disorders highlight the importance of thyroid hormones for normal growth and their multiple roles in linear growth and metabolism.

Adipokines

In addition to these hormones controlling skeletal growth, several metabolic hormones produced by adipose tissue are important in regulating body composition during childhood, through both direct effects on fat storage and indirect effects on the feelings of hunger and satiety. Leptin plays an important role in the satiety response. Often referred to as the "satiety hormone," leptin inhibits food intake and promotes energy expenditure. Insulin secretion induces leptin production and secretion. Leptin, in turn, suppresses appetite-stimulating neuropeptides, leading to its appetite regulating effects. Serum leptin levels are positively associated with adipose tissue mass in both obese children and those with a normal range of BMI.[29] Leptin levels are higher in girls, which may be due to their larger fat mass.[55] However, these differences in leptin tend to persist after adjustment for fat mass, suggesting that synthesis, transport, or clearance of the hormones differs by sex even in prepubertal children.[103]

In addition to these effects on body composition, leptin also appears to play a role in linear growth. Leptin stimulates GH secretion, acting as a metabolic signal at the hypothalamic level and also has local effects.[121] Locally, leptin stimulates chondrocyte proliferation and cell differentiation at the growth plate.[68] In animal models, leptin administration to leptin deficient ob/ob mice led to a significant increase in femoral length.[145] Further, increased levels of leptin, along with estradiol, prolactin and adrenal androgens, have been implicated in the linear growth acceleration seen with obesity in children.[145]

Adrenarche

An important endocrinological event shaping childhood growth and development is adrenarche, which typically occurs between 5 and 8 years of age. While the exact triggers are unknown, adrenarche occurs with the maturation of the *zona reticularis* of the adrenal cortex, which leads to an increased production of adrenal androgens including dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione. Adrenarche is considered a marker of the childhood to juvenile transition[45,28] and has been proposed to underlie the mid-childhood growth spurt, possibly reflecting ancestral pubertal initiation. Several issues arise, however, with this interpretation. Despite their similar timing, adrenarche and the MCGS can be dissociated. In children followed longitudinally across the mid-childhood growth spurt, for example, peak adrenal androgens levels were seen 1 year after the MGCS, suggesting that increasing androgens do not trigger the MCGS.[93] Adrenal androgens do not appear to play a large role in linear growth.[93] Finally, the timing of adrenarche and puberty are not highly correlated,[19] suggesting that they are independently controlled events.

More support is seen for an association between adrenarche and the adiposity rebound. One of the actions of DHEA is to stimulate the uptake of glucose by adipose cells, particularly in abdominal adipose tissue and muscle cells.[19] Thus, adrenarche may be associated with a shift in metabolism that promotes the increase in adiposity seen during later childhood. While the exact mechanisms linking adrenarche to these changes in metabolism and body composition are unknown, DHEA interacts with leptin in both sexes and IGF-1/GH in girls.[38] For both sexes, leptin stimulates the production of DHEA.[12] In girls, GH/IGF-I may also act as a metabolic signal, contributing to insulin resistance and increased adrenal androgen production.[38] These relationships between insulin, IGF-I and adrenal androgens are not seen in boys, suggesting that prepubertal estrogen production may also play a role in adrenarche for girls and may also underlie some of the sex differences seen in adipose tissue distribution.

The relationship between DHEA/S and adiposity may be a reciprocal one that shapes the timing of adrenarche. DHEA/S promotes adipose tissue deposition. Increasing adipose tissue deposition during the adiposity rebound, in turn, may stimulate adrenarche. More leptin is produced by the increased adipose tissue mass, stimulating greater DHEA/S production, contributing to the maturation of the *zona reticularis* and potentially acting as a trigger for adrenarche.[19,93] Adrenal androgens increase during early childhood, possibly as early 3 years of age,[83] with the highest one-year increase in DHEA/S coinciding with the highest one-year increase in BMI (i.e. the BMI/adiposity rebound).

Research suggests that the timing of adrenarche may be associated with weight gain in earlier childhood. Among children participating in the Avon Longitudinal Study of Parents and Children (ALSPAC), for example, children with the highest levels of DHEAS at age 8 were those who had gained the most weight between ages 0–3.[80] Similarly, the rapid catch-up growth during early childhood seen in first-generation Bangladeshi migrants to the UK was associated with earlier adrenarche.[47] In clinical samples of children, premature adrenarche, defined as the presence of pubic hair before 8 years of age for girls or 9 years of age for boys, was more likely in obese children.[69] These findings suggest that early life factors shaping weight gain may be important for the timing of adrenarche.

Environmental factors associated with childhood size

Most research on the environmental influences on human growth has focused on infancy and early childhood.[118,128] The slow rate of growth during childhood and the juvenile period leads to the perception that environmental factors have a relatively limited impact on growth during this time. However, the sensitivity of childhood growth to environmental factors is demonstrated through the variability in child growth seen globally and by the

processes leading to child stunting (low height-for-age) and catch-up growth and, conversely, overweight and obesity.

Variability in child size

The extent of variability in child growth globally has been debated, with some research suggesting that few inter-population differences are seen in growth during childhood[18,40,41] and others finding marked differences in growth trajectories.[133] For example, Haas and Campirano[40] found few interpopulation differences in child height at age 7 among children from the highest socioeconomic levels in each of the world regions. Conversely, in their comparison of 22 small-scale societies, Walker and colleagues[133] found that growth rate was variable for children aged 3−10 and proposed that the rate of growth during this time was shaped by mortality risk from infection and other extrinsic causes.

These differing findings suggest that, while the growth of pre-school aged children with favorable nutrition and environmental conditions appears to be similar regardless of genetic or ethnic background,[41] dietary and environmental conditions remain important factors shaping growth patterns during childhood. The plasticity of child growth to environmental conditions is documented by the comparison of the growth of Mayan children in Guatemala compared to Mayan children living in the United States.[14] Among Maya children aged 5−14 years of age, children born in the United States were over 5 cm taller, were heavier, and had larger subcutaneous skinfolds than children living in Guatemala, differences attributed to changing diets, reduced exposure to water-borne pathogens, improved health care, and increased opportunities for child development in the United States.[14] These factors were also emphasized by the WHO as important in their assessment of the feasibility of creating a growth standard for children and adolescents. They stressed the importance of selecting samples with adequate nutrition, low rates of infection, sufficient socioeconomic status, no evidence of continuing secular trends in height and normal birthweight since all of these factors may contribute to individual and population differences in child growth and are needed for optimal growth.[18] An additional concern was avoiding settings that would permit excessive weight gain and inflate the proportion of children with high weight for height.

The overall impact of detrimental environmental factors on growth and survival may be lower in childhood than in infancy, since nutrient needs are lower per unit of body weight and the immune system is sufficiently developed to improve survival from routine infection. Nevertheless, poor diet and environmental pathogen exposure can lead to new or continuing growth faltering in childhood, with impacts on stunting and cognitive development. Conversely, diets high in energy and fat and environments with low physical activity opportunities may contribute to increasing weight gain and the development of overweight and obesity in childhood, risk factors for later obesity and cardiometabolic

disease. The next sections review the role of these dietary and environmental factors on child growth and their implications for future health and developmental outcomes.

Stunting and catch-up growth

Available data show that malnutrition is an issue for school-aged children across LMIC settings. Almost 20% of school-aged children are stunted globally, with prevalences as high as 30%–74% in national surveys from Guatemala, North Korea, Madagascar, Malawi and Vietnam.[11] Until recently, this stunting was thought to have occurred primarily, if not exclusively, before 2 years of age.[131] Interventions aimed at improving stunting have increasingly focused on this early time period.[131] Certainly, the first 1000 days is critical for the development of linear growth faltering. Globally, 17%–40% of linear growth faltering is already present at birth[60] and worsens across early childhood with the introduction of poor-quality complementary foods and repeated childhood infections.[147] Comparison of the growth of children from 54 countries shows a general pattern of length-for- age (LAZ) faltering from early infancy through 24 months, with little to no consistent change after this time point.[132] However, recent cross-national comparisons document that both stunting and catch-up growth, accelerated growth following disruption that reduces overall height deficits,[61] may occur during childhood into adolescence. The potential for stunting to newly occur and/or improve provides evidence that environmental exposures continue to influence growth throughout childhood.[60,88]

Findings from the Young Lives Study, the Consortium for Health Oriented Research in Transitioning Societies (COHORTSs) collaboration, and rural Gambia, all conducted in LMIC, suggest that both growth faltering and recovery continue beyond 2 years of age. In their longitudinal analysis of the growth of children participating in the Young Lives Study from Ethiopia, India, Peru and Vietnam, Lundeen and colleagues (2014) document high levels of stunting from 6 to 18 months, but also show that height-for-age (HAZ) continues to decline until age 5 in three of the participating countries. They also documented that, while HAZ was correlated across the 1, 5 and 8 year waves, a substantial proportion of the variability in HAZ at ages 5 (40%–74%) and 8 (27%–47%) was not predicted by HAZ at the earlier times,[65] indicating that growth during childhood remains sensitive to environmental and/or gene *x* environment effects. Results from the older cohort of Young Lives Children show that growth faltering continues across later childhood and adolescence.[35] In their analysis, Fink and Rockers[35] document considerable movement in child HAZ between 8, 12 and 15 years of age, with nearly half of children (45%) experiencing a 0.5 SD increase or decrease in HAZ between study rounds. The likelihood of change did not differ between 8–12 years and 12–15 years, leading the authors to conclude that these changes were not all attributable to the pubertal growth spurt. Of those who were stunted at age 15, nearly one-third were not stunted at age 8, suggesting that

growth faltering is not limited to infancy and early childhood and that a large proportion of children continue to experience, or newly experience, growth faltering during childhood.

Longitudinal data from COHORTS and rural Gambia document that catch-up growth is also possible during this period even without intervention. Prentice and colleagues[88] show that substantial catch-up growth occurs between 24 months and mid-childhood (ages 4–5) and again between mid-childhood and adolescence in both samples. Among the COHORTS samples, four of the five cohorts (Brazil, Guatemala, South Africa and Philippines) showed evidence of catch-up growth from 24 to 48 months. In addition, three of the cohorts (Guatemala, India and Philippines) showed catch up growth between mid-childhood and adulthood, with an average "catch up" of nearly one HAZ score across childhood period. Similar patterns were seen in the Gambian samples with even greater height gains, nearly 2 HAZ-scores. The greater catch-up seen in children with larger deficits may indicate that these results stem from regression to the mean; however, the COHORTS findings come from analyses that condition anthropometric measurements on the previous measurement to control for this tendency.[116] The Young Lives Study findings showing considerable catching up and falling behind during childhood described above [35] also supporting the interpretation that these findings represent true variability in physiological responses to environmental context rather than a statistical artifact.

Other methodological challenges have been raised to the idea that growth faltering plateaus at age 2.[60,88] The data presented by Shrimpton and colleauges[112] and Victora and colleagues[131] that most strongly support the idea that the window for intervention closes at age 2 show troughs in data at 24, 36, and 48 months, a pattern that may indicate that age is poorly estimated in some of the included samples. Rounding up to these ages may make children appear smaller than they actually are and underestimate the potential for catch-up growth.[88] A broader critique has been made about the use of HAZ as an indicator of linear growth faltering and catch up growth.[60] The standard deviation of HAZ increases with age; thus, changes seen in HAZ may be due to either changes in the magnitude of the difference between a child's height and the standard (the numerator) or due to changes in the SD with age (the denominator). Leroy and colleagues[60] argue that using HAZ masks the degree of accumulation of height deficits across childhood as HAZ does not directly correspond to absolute change in height across age. Absolute differences in height (HAD) between the participants and WHO growth standards show a very different pattern of growth faltering than that seen for HAZ in their analysis of DHS datasets. As in other analyses,[131] HAZ dropped steeply between 18 and 24 months, with little to no additional deterioration up to 5 years of age. Conversely, among the same children HAD continued to worsen through 60 months with no sign of stabilization or improvement in early childhood (i.e. between 24 and 60 months[60]). Based on this analysis, they argue that as much as 30% of the total growth deficit seen may accumulate after age two.

The use of absolute measures vs. z-scores and even the importance of catch-up growth in childhood are not without debate;[30,132] however, examination of the impacts of diet and other environmental exposures on growth during this time provide further support for the continuing plasticity of growth during childhood and the possibility of catch up growth. Historic studies of child malnutrition during the World Wars document that even long periods of childhood starvation can be followed by catch-up growth and that complete recovery is possible with refeeding.[109] On a population-level, undernutrition and reduced caloric intake are associated with diminished growth velocity and short stature during childhood, and much of the growth faltering and short stature seen in LMIC is attributed to widespread undernutrition due to poor diet diversity.[30]

The growth impacts of malnutrition during childhood likely stem from the reduced plasma levels of insulin, insulin-like growth factor-1 (IGF-1), thyroid hormone, and leptin and the increased levels of glucocorticoids and IGF-binding protein (IGFBP)-1[145] seen with undernutrition. Protein's effects on child growth, for example, are likely mediated through the production of IGF-I. IGF-1 is sensitive to changes in nitrogen balance and its secretion is thought to be regulated by amino acids directly and through insulin-dependent pathways.[120] Severe protein malnutrition is associated with reduced IGF-I production[145] and, conversely, milk consumption appears to be associated with increased IGF-I levels in childhood.[95] Population-based studies support an association between higher protein intakes from animal source foods, including meat and milk, and improved height growth on a population level.[74,104] Ugandan herder children, who consume milk and meat, for example, are significantly taller and thinner than neighboring farmer children, who consume mainly plantains.[104]

Although the effectiveness of generalized nutritional interventions aimed at increasing energy intake to improve linear growth and reverse stunting appears limited even in infants and young children,[62] clinical interventions have shown the potential for height restitution throughout childhood for children suffering from nutritional conditions limiting energy intake or GH deficiency.[109] A recent systematic review also supports an association between supplementation with protein, zinc and vitamin A and improved linear growth after the age of 2, particularly in children who are severely stunted.[97] Several studies document that supplementation with animal source foods improved growth better than foods with similar energy but lower protein. New Guinean children supplemented with skim milk, for example, gained almost 1.5 cm more in height during follow-up than control children or those supplemented with a similar energy intake from fat (margarine) and 1 cm more than children supplemented with a 50% greater energy intake from carbohydrates (taro).[66] More recently, supplementation with two eggs per day improved the growth of rural Ugandan children participating in school feeding program.[5]

Micronutrient supplementation, including supplementation with multiple micronutrients, zinc, and vitamin A, is linked to improved child growth in height and length.[97,128] Zinc has been shown to improve linear growth and weight gain in children in a number of LMIC settings.[97] Zinc supplementation in Thai school children, for example, was associated with greater gains in height and improvements in HAZ than a control group over a 6-month period.[94] Although no differences in weight or BMI were seen between the supplemented and control groups among the Thai children, a large study of children aged 2−10 in Taiwan showed improvements in height, weight, BMI and appetite ratings among supplemented children who had low initial serum zinc levels (<75 μg/dL).[24] These effects of zinc on linear growth and BMI likely stem from its wide-ranging roles in cellular growth, differentiation, and metabolism, including its promotion of growth hormone production, chondrogenesis, osteoblast function and bone calcification.[97] On its own or combined with zinc, vitamin A supplementation has also been shown to improve linear growth in school-aged children suffering from vitamin A deficiency.[97,140] Like zinc, vitamin A plays an important role in immune function, and the improvement in linear growth in supplemented children may be attributed to a reduction in diarrheal and respiratory infection morbidity.[11]

The important roles of micronutrients in immune function highlights the close association between nutritional status, infection and growth in school-aged children. The improvements in growth seen in the COHORTS and Young Lives studies in the absence of intervention has been attributed to the maturation of children's immune systems, particularly the development of the adaptive immune response to previously encountered pathogens. This improved immune function reduces the frequency and severity of growth-impairing infections in school-aged children.[88] However, frequent infections and chronic pathogenic exposures may nevertheless induce inflammation and limit children's ability to grow to their potential or catch up from earlier growth deficits. Anthropological investigations of the growth of indigenous South American populations document patterns of growth that differ significantly from WHO references.[130] Among the Shuar, an indigenous Amazonian group, for example, children experience progressive decreases in height across childhood with child-juvenile median growth rates that are around 1.0 cm less per year than WHO references for height for both boys and girls.[130] These divergent growth patterns appear to be linked to the high pathogenicity of the Shuar's environment; frequent infection with helminths and immune system activation, alongside low-energy density diets, limit the resources needed for growth.[13]

Taken as a whole, the literature on the etiology of stunting reaffirms the importance of early life exposures. Nevertheless, historic and recent research shows that growth remains plastic during childhood into adolescence. Improving the nutritional and health environment of children may prevent new or continued growth faltering, and the window for intervention may extend into these years as well. Given the short- and long-term

consequences of stunting, discussed in more detail below, additional attention on this period of growth is warranted.

Overweight and obesity

On the other end of the malnutrition spectrum, weight gain in childhood has received considerable attention. Unlike height, child weight shows pronounced sensitivity to environmental and social conditions.[21] Early and middle childhood, particularly around the time of the adiposity rebound, may serve as an important window for the development of later obesity and also cardiometabolic disease.[22] Childhood and adolescence are also sensitive times for food preference and eating pattern development,[70] with consequences for long term health outcomes.

Globally, the prevalence of child overweight, BMI ≥85th percentile and <95th percentile, and obesity, BMI ≥95th percentile, have been increasing. Over the past forty years, the global mean age-standardized prevalence of obesity in children and adolescents, aged 5−19, has increased from less than 1% in 1975 to 5.6% in girls and to 7.8% in boys in 2016.[76] Rates of overweight and obesity vary considerably between countries with the highest levels (at or above 20%) seen in some countries in Polynesia and Micronesia, the Middle East and north Africa (eg, Egypt, Kuwait, Qatar, and Saudi Arabia), the Caribbean (Bermuda and Puerto Rico), and in the United States. While lower rates of obesity were seen Western Europe and parts of Africa,[76] the rate of change differed markedly between these sites. Africa has the greatest percent increase in child overweight and obesity, albeit at very low rates. Conversely, the increase in obesity seems to have lessened or even plateaued in some high-income settings.[79]

The distribution and patterns of change in childhood obesity differ within and across contexts. Cross-national comparisons from nine countries, Australia, China, England, France, Netherlands, New Zealand, Sweden, Switzerland and US, show that, while the rate of child obesity appears to be stabilizing, the prevalence at which countries are stabilizing varies considerably, from 13.5% in France to 37.4% in the US.[79] Both within and between countries, the prevalence of obesity and patterns of change also differ by child sex, age, and socioeconomic status. Stabilization appears to be more marked in girls compared to boys and younger (2−5 years) versus older (6−11 or 12−15 years) children. In this study and others, the pattern of obesity with socioeconomic status varies across contexts. In South Asia, for example, the prevalence of overweight and obesity is positively associated with household socioeconomic status[72] whereas in Western Europe and the United States the reverse pattern is seen.[42,78] Within the United States, the prevalence of child obesity also varies by race/ethnicity, with Hispanic, 25.5%, and non-Hispanic black, 22.0%, children being disproportionately affected compared to non-Hispanic white, 14.1%, children.[36,42]

Geographic and sociodemographic differences in the prevalence of obesity have been attributed to a number of environmental factors, particularly the availability and over-consumption of high-fat, energy-dense foods and limited physical activity. In the United States, fewer than 1% of children and adolescents meet the requirements for ideal diet quality and fewer than half meet the requirements for intermediate diet quality.[64] When compared to recommendations, the intake of whole grains and fruit consumption remains below recommendations and sodium consumption is considerably higher. Almost 60% of American children and adolescents, aged 2−18, do not meet the recommended number of servings of fruits per day while 90% do not meet recommendations for vegetable consumption.[54] Importantly, inequities are seen in diet quality by race/ethnicity, income and parental education. In the United States, black and Mexican-American children, for example, had lower-quality diets compared to white children, and diet quality increased with parental educational attainment.[64] These patterns stem from the unaffordability of healthy food options, which can promote social inequalities in overweight and obesity.[32]

Changing patterns of consumption, such as greater consumption of foods outside of the home, increased portion size, increased snacking, and greater sugar-sweetened beverage (SSB) consumption have contributed to increased caloric intake for children in the US and globally.[87,106] Children and adolescents are consuming more of their foods away from home. In 2016, 91% of American parents reported purchasing at least one fast-food meal for their child in previous week.[43] At the same time, the portion size of most restaurant and ready-to-eat foods has expanded over the past 30 years, making it difficult to prevent excess energy intake.[7] Increased snacking frequency also accounts for a considerable amount of the energy consumed by children[148] and is a risk factor for overweight and abdominal obesity.[75] The prevalence of snacking varies across countries; however, most studied countries have seen an increase in snacking and the proportion energy coming from snacks, particularly among younger children.[86] Over 95% of 4−13 year-old children in the United States and Australia had consumed snacks in the previous 24-h, accounting for one-quarter and one-third of their total energy intake (TEI), respectively compared to 76% of Mexican children and 65% of Chinese children, proving 15% and 10% of their TEI, respectively.[134] In addition to the added energy provided by snacks, savory snack consumption has been linked to excess sodium intake.[134] Along with sodium-heavy snacks, added sugars from beverages remain a problem for children in the United States and elsewhere.[67,117] In both Mexico and the United States, for example, SSBs contribute over 20% of the total daily calorie intake and SSB are one of the highest sources of calories for Mexican children and adolescents.[117] Since soda consumption is linked to perceived and actual water quality, children living in households with poor water quality may be at increased risk for higher sugar intakes and obesity.[81,96]

Alongside these changes in diet intake, physical activity patterns have also undergone changes in many high and LMIC contexts. Historically in high income countries and

currently in many countries undergoing the nutrition transition and economic development, the types of activities that children engage in have shifted with the incorporation of modern labor-saving devices, less reliance on the subsistence labor of children and more sedentary lifestyles.[89,126] Other changes, such as lower reliance on walking or bike-riding for transportation, fewer opportunities for physical activity in schools, and increased screen time, have also reduced the number of children meeting the Physical Activity Guidelines for Americans. Only 24% of American children aged 6−17 met physical activity guidelines in 2016, with differences seen by sex, age and socioeconomic status. Boys, younger children (6−11) and children living higher income households had higher levels of physical activity than girls, older children (12−19 years) or children from lower income households.[154]

Another factor inhibiting adequate physical activity during childhood is daily screen time. Similar to obesity risk, amount of daily screen time increases with age. International comparisons suggest that television viewing is a type of sedentary behavior that is more strongly associated with obesity than measures of overall sedentary time,[53] suggesting that obesity related to physical inactivity may increase with the expansion of television and other devices in LMIC. Findings from the China Health and Nutrition Survey shows that, while children's leisure time physical activity and screen time are associated with that of their parents, the magnitude of this association is weakening over time as children's access to spending money and screens are increasing with economic development.[149]

Although energy imbalance from energy-rich diets and limited physical activity contribute to obesity at the individual level, the limited efficacy of interventions aimed at improving child weight status or reducing the incidence of overweight at the individual level document the importance of social, cultural, and physical environmental influences in the development of child obesity. Child weight status is influenced by social determinants of health, such as food access, school food environments and SES. Low SES neighborhoods in the US are more likely to have limited access to supermarkets and to have greater numbers of convenience stores and fast food restaurants.[73] This type of environment limits children's ability to access healthy foods while subsequently increasing their access to high-calorie, low nutrient snacks and beverages.[90] Poverty and food insecurity contribute to undernutrition and poor health outcomes for children. Children living in food insecure households in the US have been shown to have poorer diet quality, have less food available at home, less frequently consume breakfast, and eat a greater percentage of energy from fat than food secure youth.[141] These dietary differences may be more pronounced among older children and adolescents, who are less buffered by school programs or may alter their diets to protect younger siblings. This seemingly paradoxical relationship between food insecurity and obesity is increasingly seen in LMIC contexts

and is linked to the increasing availability and affordability of high-energy, processed foods with economic development and increased global market integration.[34]

In addition to the importance of the multiple socioecological levels —household, community, and geopolitical— in the etiology of child obesity, cultural norms are also important for shaping child diet and obesity risk. Parents' ethnotheories, culture-specific beliefs and norms, about appropriate child body size, eating behaviors and diet quality[6,17] shape parental behavior and link broader social changes, such as nutrition transition and modernization, to individual child growth. For example, Brewis[17] documents how cultural values that chubby children are considered healthier in a transitional economy where under-nutrition among children is still common and the tendency of working parents to show love through sweets and snacks may contribute to obesogenic child diets in a dual burden context in Mexico. Gender-specific expectations may also differentially shape obesity risk for boys and girls. Among low income children in Appalachia, boys were more likely to spend leisure time watching television or playing computer games than girls who did more physical activity through household chores.[27]

In summary, rates of childhood overweight and obesity are high globally and continuing to increase in LMIC. Childhood obesity has negative mental and physical health consequences throughout the life course. Obese children are more likely to be bullied and face discrimination. They are also more likely to become obese adults and develop comorbidities, such as diabetes and cardiovascular diseases.[106] Thus, addressing the interactions between nutritional, behavioral, and environmental factors is needed to decrease the prevalence of childhood obesity.

Childhood growth and long-term health

Although comparatively less research has focused on the pre-adolescent, childhood period, than earlier and later stages of growth, this period is also an important one for shaping both adult stature and cognitive function[11] and adiposity in adolescence and adulthood.[22] Both under- and overnutrition during the school-aged years can have detrimental impacts on development and long term-health. Finally, a growing body of research links the pattern of linear growth and or weight gain during childhood to a number of health outcomes in later life, including cardiovascular disease, reproductive cancers, and mortality risk.

Short- and long-term health consequences of undernutrition

In the short-term, childhood stunting and undernutrition have been associated with poorer health, reduced intellectual achievement and poorer school performance. Recent papers have questioned whether stunting and developmental outcomes are causally linked,[62]

citing a lack of for causal mechanisms linking stunting to cognitive development, work capacity or chronic disease risk. Nevertheless, growth faltering and cognitive development both stem from deficient environmental conditions, including suboptimal nutrition, inadequate care and repeated infections, which may underlie poorer outcomes seen in stunted children.[62,30] Stunting in early childhood has been consistently linked to poorer cognitive performance and lower school achievement during childhood,[150] including a reduction in years of completed schooling, an older age at school enrollment, and a greater likelihood of failing a grade.[151] Relatively few studies have examined the impact of continued growth faltering or, conversely, catch-up growth during middle or late childhood on cognitive outcomes. However, findings from the Young Lives Study and the Tsimane' project among indigenous Amazonian children suggest that growth in later childhood is also associated with developmental and educational outcomes.[35,129] Recovery from earlier stunting, for example, led to similar school attainment as children who were never stunted among the Tsimane',[129] suggesting that human capital outcomes can be improved with intervention during childhood.

These associations between poor environmental conditions, child health and academic outcomes are also seen in high income settings. In the United States, food insecure children are more likely to have chronic health conditions and are more likely to have their health rated fair/poor by caretakers than food-secure children.[84] Food insecure children have higher rates of asthma diagnoses, report headaches and stomach aches more frequently, and have more emergency room visits,[2,125] which contributes to greater school absenteeism and tardiness.[84] In addition to these health conditions that may limit school attendance, most examined behavioral, emotional, and academic problems are higher in children experiencing food insecurity or hunger. Children from food insecure households have lower math scores, are more likely to repeat a grade, are more likely to have seen a psychologist and have more difficulty getting along with peers than those from food secure households.[2,50,110] While stunting may be unlikely to occur from undernutrition in high income settings, these studies suggest that the poorer child health and behavioral problems that accompany undernutrition and poverty can have important consequences for children's academic performance and social development.

In addition to these potential consequences for academic development, stunting during childhood is associated with smaller body size in adulthood, a risk factor for reduced work capacity for men and women[3] and obstetric complications and poorer birth outcomes in women.[11,62] In places were physical labor is required for food production, reduced work capacity has the potential to limit food availability,[114] contributing to an intergenerational cycle of malnutrition and poor growth. For women, short stature is associated with increased risk of obstetric complications, such as cephalo-pelvic disproportion and

obstructed labor, due to smaller pelvic size.[11] The infants of short mothers are more likely to be born as small-for-gestational age (SGA), likely due to maternal physical and nutritional constraints.[1] Consequently, short maternal stature is associated with increased risk of neonatal and infant mortality, increased child morbidity, and intergenerational transmission of stunting.[25,57] Given the potential for these long-term consequences and intergenerational effects of poor growth during childhood, efforts to improve health and nutrition throughout the life course, not just infancy and early childhood, are needed to improve linear growth and long-term potential.

Child obesity, adiposity rebound and long-term outcomes

The high prevalence of child obesity seen in countries like the US has raised alarm, since obesity during childhood has the potential to become a life-long health problem. Over 50% of obese children become obese adults,[113] with increased risk for the development of cardiovascular and metabolic conditions.[91,92] The importance of obesity during childhood versus other periods, such as infancy or adolescence, for predicting adult obesity risk, however, remains debated.[37]

Systematic reviews provide evidence for a moderate to strong degree of tracking across childhood and adolescence.[48] Certainly, higher weight gain across the period of infancy through adolescence is associated with higher adult obesity risk.[85] This association of larger size in early life with larger size in later life may reflect a genetic propensity to obesity, epigenetic programming or the tracking of adiposity-related behaviors. However, a number of studies suggest that timing of weight gain may be associated with a differential risk of later obesity and/or cardiometabolic disease.[135] A systematic review by Owen and colleagues,[82] for example, shows that childhood adiposity from ages 7–9 is predictive of cardiovascular disease, with only weak, negative or null associations seen at earlier ages. Supporting the importance of middle childhood for the development of later adiposity and cardiometabolic disease are recent genetic studies that document a shift in BMI biology around this time. FTO, a gene variant commonly associated with obesity, for example, was associated with BMI from only age 7 onward in a longitudinal analysis of common gene variants and BMI across childhood.[44]

In particular, the timing of the adiposity rebound may influence the risk of future obesity and cardiometabolic disease. Since Rolland-Cachera and colleagues' 1989 paper[100] documenting that the age of AR and the magnitude of BMI at the AR were risk factors for non-communicable disease in later life, consistent associations between earlier rebound and higher BMI in adolescence and adulthood across a number of settings (reviewed in Campbell[20]). For example, early AR was associated with higher BMI and greater waist circumference in young adult participants in the Dunedin Cohort Study in New Zealand.[143]

More recent research has established that early AR (<5.4 years) is associated with higher BMI and fat mass measured by DXA in German adolescents and young men, aged 18–20.[77] Longitudinal follow-up at age 15 in over 500 ALSPAC participants documented a strong dose response between the timing of AR and BMI and FMI, independent of a range of confounders,[146] providing strong evidence that the timing of AR is associated with later adiposity across a range of timing and adiposity measures.

The association between earlier age at AR and later cardiometabolic disease, including diabetes and cardiovascular disease, suggests that early rebound may be part of a developmental pathway leading to metabolic dysregulation.[20] In the Helsinki Birth Cohort, participants with AR before 5 years of age had a higher incidence of type 2 diabetes in adulthood compared to those who had AR after age 7.[33] More recent research documents that the timing of AR may be associated with altered cardiometabolic markers earlier in life. Among 12-year-old Japanese children, earlier AR was associated with higher plasma triglycerides, atherogenic index, ApoB and blood pressure and lower HDL-C in boys.[56] The timing of AR was only significantly associated with ApoB in girls, indicating that the association between AR and cardiovascular measures may show sex differences. Studies of American adults, on the other hand, show that the timing of AR is inversely associated with systolic and diastolic blood pressure for both men and women.[105] These contrasting results may derive from the differences in the ages measured or the sample populations. Alternatively, these sex differences in developmental milestones like the age at AR, adrenarche or the transition from middle childhood to juvenile growth may reflect different energetic constraints for boys and girls.[45]

The observations linking AR to cardiovascular measures have led a number of researchers to suggest that the period of AR may be a critical one for the development of later disease.[28] However, other researchers have criticized these associations as stemming from statistical artifact,[26] claiming that early AR predicts later adiposity only because it identifies children who already have high BMI or who are crossing BMI centiles upward. Other studies looking at trajectories of weight gain and/or BMI change across childhood have found that rapid gains in BMI during childhood may be more important for the development of overweight than the timing of AR or even given BMI at any age. Findings from a large population-based study found that among adolescents who were overweight or obese, most excess weight gain occurred between 2 and 6 years of age compared to normal weight adolescents, whose BMI z-score remained stable throughout childhood.[37] Similarly, a rapid increase and greater variability in BMI during childhood was associated with increased obesity measures in adulthood, independently of mean BMI during childhood.[63] Together, these studies indicate that a steady pattern of BMI is important for the development of healthy trajectories.

Growth trajectories and health

More generally, trajectories of linear growth and BMI during childhood have been linked to the development of a number of different diseases in adulthood. Linear growth may be important for the development of obesity and other conditions in adulthood. In a longitudinal, multicenter study, large height differences were seen at 9 and 11 years of age in those who went on to develop obesity by age 18, suggesting that faster height growth in children who become obese may be a sign of accelerated physical maturation.[119] Such mechanisms may also underlie the association of more rapid linear growth and greater final height with adult cancer risk seen in several studies. Among British women, height velocity at ages 4–7 and 11–15 were independent predictors of greater breast cancer risk.[31] Similarly, Danish women who were overweight or tall at ages 7 and 13 had elevated risk of ovarian cancer compared to girls who were not tall or were not overweight at both ages.[152] Linear growth trajectories during childhood have also been linked to cardiovascular risk factors in LMICs. Findings from the Velore, India birth cohort show that individuals with greater linear growth during childhood and/or who were taller as adults had higher cardiovascular risk factors including greater waist circumference, blood pressure, insulin resistance, and cholesterol.[153] While the exact mechanisms underlying the associations between faster linear growth and increased cardiometabolic and cancer risk remains unknown, together, these results suggest that the tempo of maturation affecting both linear growth and body mass, rather than the timing of AR *per se*, may be particularly important for later health outcomes.

Summary

While receiving less attention in the health and human biology literature, growth during childhood is nonetheless an important period for long-term developmental and health outcomes. Growth during this period, albeit slower than either infancy or adolescence, remains sensitive to environmental exposures, such as diet, physical activity and pathogens. In addition, hormones become increasingly important for regulating growth and development during this time. Their sensitivity to environmental cues and energy availability make them important proximate biological mechanisms shaping life history trade-offs during this period, as evidenced in the widening in sex differences in growth and body composition. Considerable debate remains about the potential for interventions to improve linear growth during childhood. However, the importance of linear growth for long term health and the associated consequences of undernutrition on cognitive development and academic achievement suggest that this period should not be ignored. Further, the importance of childhood obesity in the establishment of unhealthy weight trajectories and cardiometabolic risk highlight the critical importance of nutrition and

physical and social environmental context experienced during childhood for shaping long-term health. More research is needed to fully understand this important phase of the life cycle.

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CHAPTER 4

Adolescent growth

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Introduction

Adolescence is the period of transition from childhood to adulthood. There is no single event that marks the boundaries of this period of major psychological and biological changes, but it is generally assumed that adolescence starts with the onset of a growth spurt and spans the "teenage" years. The notable growth spurt is perhaps the most visible sign, along with the appearance of secondary sexual characteristics during pubertal maturation. Puberty refers to the developmental phase where the child will reach reproductive capacity, and covers approximately the first half of adolescence. At the end of this period, most children will have also reached their final or mature size for most skeletal dimensions, and may have surpassed their parents in height when a positive secular trend exist. In this chapter we will focus on physical or somatic growth during adolescence as opposed to behavioral or psycho-social changes, or the sexual maturation during puberty which is described elsewhere in this volume (See Chapters 1, 5, and 12). Children increase considerably in size during this period, and the timing of this increase, called the "tempo" of growth (see Chapter 1) is variable. Consequently, large differences in size may occur between children of the same chronological age. Another consequence is that the growth pattern of individual adolescents will generally differ from the average growth curve, a phenomenon that is closely related to the features of longitudinal and cross-sectional growth charts. This will be demonstrated using mathematical models that have helped to describe individual growth patterns and contributed to the analysis of the dynamics of the growth process. We will conclude with an analysis of the different growth patterns observed in boys and girls during adolescence, a period during which substantial size-differences between both sexes develop.

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The adolescent growth cycle

Growth at adolescence is characterized by the presence of an adolescent growth spurt (AGS) for many skeletal dimensions, weight, and for soft tissues such as muscle and subcutaneous fat. This spurt is initiated by hormonal changes that occur at the end of childhood that also cause the onset of sexual maturation. The timing, duration, and magnitude of the AGS vary considerably between populations and between individuals within a population. The consequences of variations in tempo on the height of children relative to their peers will be discussed later. In this paragraph we will focus on four patterns of growth that illustrate how the body changes in size during adolescence; growth in height, weight, BMI, and head circumference.

Height

A typical example of the growth in height between 1 month and 18 years of age is shown in Fig. 4.1 for a girl from the Belgian Growth Study of the Normal Child.[1–3] The upper curve is a plot of height-for-age (distance curve), while the lower curve shows the corresponding increments in height, scaled to a whole year (annual growth velocity). Annual growth velocities or yearly increments are the average velocity over the considered interval. In physics, the term "velocity" refers to the first derivative of a smooth distance curve at a particular point in time, which is equivalent to the velocity at precisely that point, i.e. instantaneous velocity. In growth research, this concept is difficult to work with, because studies of the size of body segments at daily or weekly intervals, with high precision techniques (for instance knemometry of the knee-heel distance with a measurement error of about 0.1 mm) show that the underlying growth process is, at micro-level, not as smooth as we usually assume[4,5] (Chapter 18). In addition, instantaneous velocity is also impractical for most body dimensions because the measurement error would exceed the observed change in growth. The horizontal bars in the velocity chart indicate the length of the intervals over which the increments were calculated. It is common practice to calculate increments from measurements not less than 0.85 years and not more than 1.15 years apart, and to scale them to *whole-year* increments (cm/year) by dividing the difference between the two measurements by the duration of the interval (i.e. distance/time). Increments calculated over a shorter interval are relatively more affected by measurement error and to a lesser extent by seasonal variation in growth.[6] Increments over intervals larger than one year would smooth out age trends.

The growth pattern in height is characterized by a gradually decreasing velocity during infancy and childhood, until there is a substantial acceleration that marks the beginning of the AGS in late childhood or the early teens. Before adolescence, considerably smaller

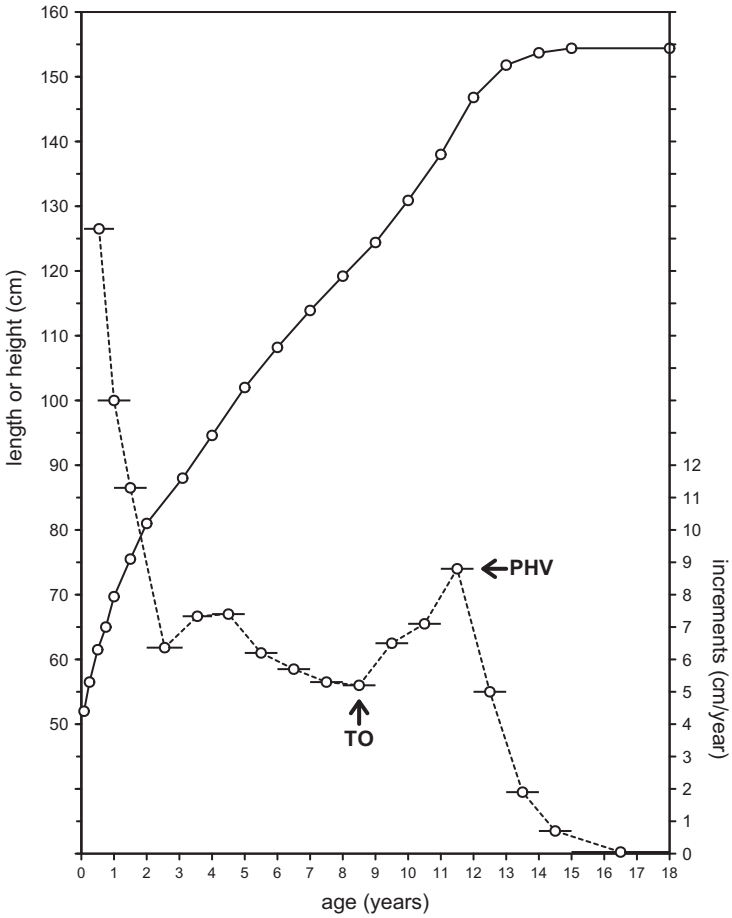

Fig. 4.1

Growth in height of a Belgian girl between birth and 18 years of age. The upper curve is a plot of height-for-age (distance curve), and the lower curve shows the corresponding annual height increments (velocity curve). Horizontal bars indicate the length of the interval over which the increment was calculated. TO (take-off) is the inflection point of the velocity curve that marks the start of the adolescent growth spurt. PHV (Peak Height Velocity) is the maximum growth velocity during adolescence. (Girl No. 29 from the Belgian Growth Study of the Normal Child[1–3]).

mid-childhood spurts may be observed in some, but not all, children[7,8] (Chapter 3). The adolescent growth spurt is however a ubiquitous feature of the normal growth curve, that will always be observed when measurements are taken at appropriate intervals.

The age at minimal velocity before puberty is considered as the onset of the AGS, and is termed as the *age at take-off* (TO). The age at take-off varies considerably between populations, between individuals within a population (the SD is about 1 year), and between sexes (the AGS starts on average 2 years later in boys than in girls). Maximum

velocity in height (or peak height velocity, PHV) is generally reached 3−3.5 years after the onset of the growth spurt. At this age, boys can grow more than 11 cm per year, and girls more than 9 cm per year. Age at take-off and age at peak velocity are useful milestones for the study of the timing and duration of the adolescent growth spurt. After having reached a peak, the growth velocity decreases rapidly, signaling the end of the growth cycle at near final height, which occurs around 16−17 years in girls and around 18−19 years in boys in Western populations. After this age, growth may continue until the late twenties, but the additional gain in height will be small (significantly less than 1 cm/year). There is a wide variation between populations, between individuals and between the two sexes as to the attained size at each age, the timing of events such as the AGS and the age at which final height is reached. The growth curve of height shown in Fig. 4.1 is typical for all post-cranial skeletal dimensions of the body.

Weight

The pattern of weight gain during adolescence is different from that of height because the start of the adolescent spurt in weight does not coincide with the age at minimal velocity in weight before puberty. Children typically show the lowest annual increase in weight in late infancy or early childhood, i.e. around 2−3 years of age.[9,10] Thereafter, the weight gain accelerates steadily but slowly until a sudden rapid increase in velocity marks the onset of the adolescent spurt in weight. The typical features of growth in weight and weight velocity are illustrated in Fig. 4.2. The sudden increase of the weight velocity that marks the onset of the adolescent spurt in weight occurs in this example at about 11.5 years of age. Determination of the precise age is however more problematic and subjective than estimating take-off for height because there is no point of inflection.

Body mass index (BMI)

Closely related to weight is the Body Mass Index (BMI), which is an anthropometric index of weight (kilograms) divided by the height (meters) squared (kg/m^2). Before adolescence, the BMI curve fluctuates, with a sharp increase in early infancy, and subsequently a decline in early childhood, until a local minimum is reached between 4 and 7 years of age (the "*adiposity rebound*"). During late childhood and adolescence, the BMI increases steadily until a maximum is reached in late adolescence or early adulthood.[11] In clinical practice and epidemiological studies, BMI is often preferred to weight, because it corrects for linear body dimensions, and can therefore be used as an index for excess body weight. The BMI is related to the composition, rather than the dimensions of the human body, and will be further discussed in chapter 19.

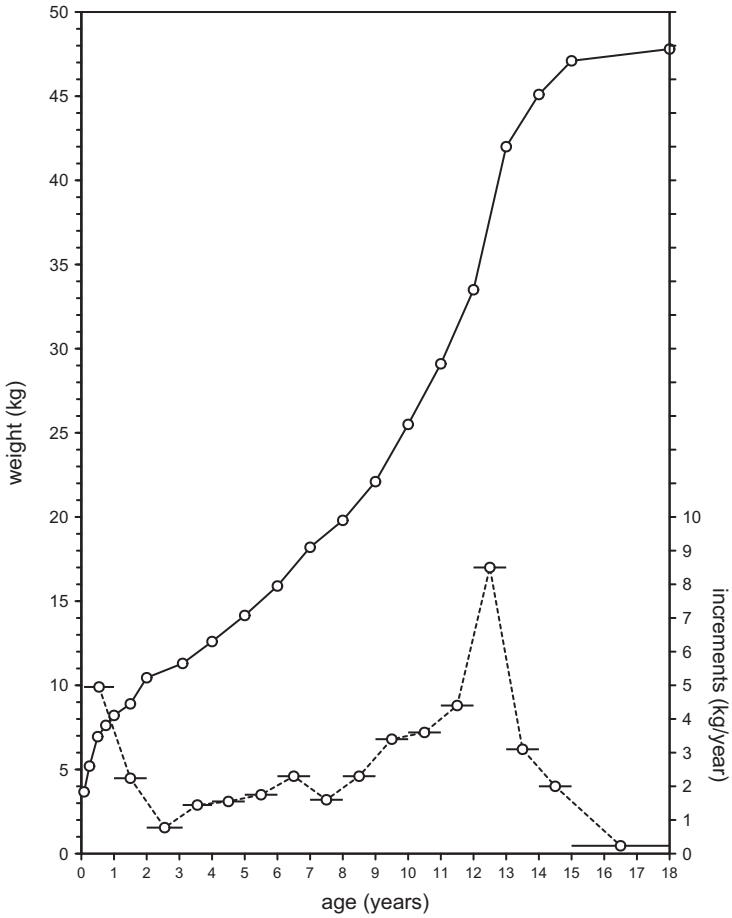

Fig. 4.2
Growth in weight of a Belgian girl between birth and 18 years of age. The upper curve is a plot of weight-for-age (distance curve), and the lower curve shows the corresponding yearly weight increments (velocity curve). Horizontal bars indicate the length of the interval over which the increment was calculated. There is a clear spurt in weight during adolescence, but no inflection point that marks the start of this growth phase. (Girl No. 29 from the Belgian Growth Study of the Normal Child[1–3]).

Head circumference

A fourth pattern of growth is seen in the dimensions of the head. Fig. 4.3 shows the growth in head circumference from birth to adulthood, as observed in the same Belgian girl we previously studied. The head grows very rapidly during the first postnatal year (the increase in head circumference is on average 12 cm in boys and 10 cm in girls), but the growth velocity in head circumference falls rapidly to levels below 1 cm/year by the age of 2 years. Thereafter the head circumference increases between a few millimetres and

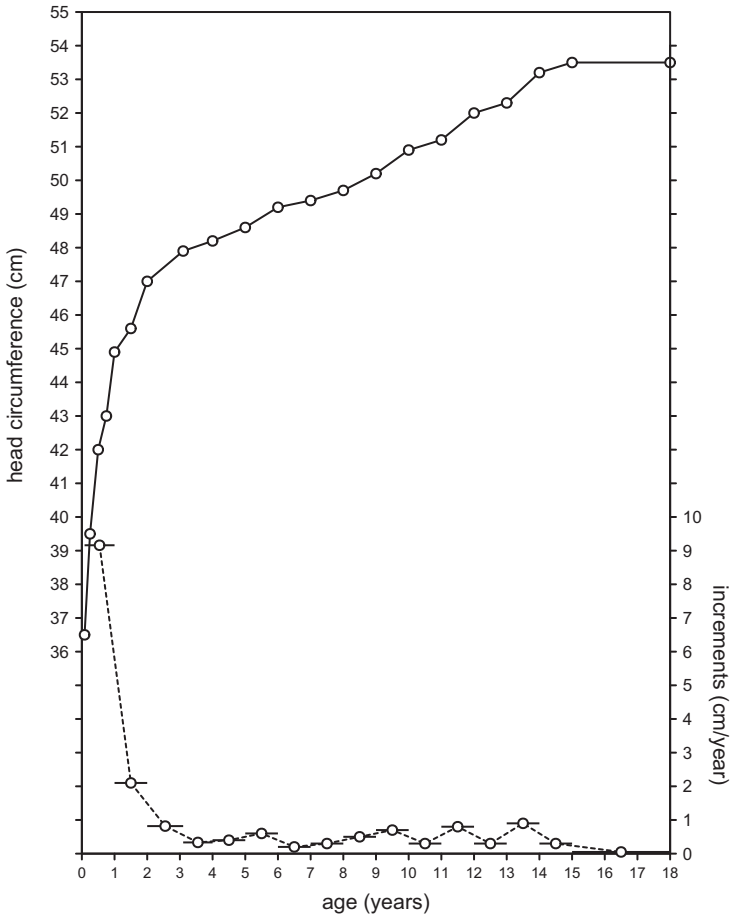

Fig. 4.3

Growth in head circumference of a Belgian girl between birth and 18 years of age. The upper curve is a plot of head circumference-for-age (distance curve), and the lower curve shows the corresponding yearly increments in head circumference (velocity curve). Horizontal bars indicate the length of the interval over which the increment was calculated. (Girl No. 29 from the Belgian Growth Study of the Normal Child[1–3]).

1 cm/year without a noticeable growth spurt in childhood or adolescence. Approximately half the post-natal growth in head circumference occurs during the first year and, as observed in the given example, almost 90% of the adult head circumference is reached by the age of 3 years. This pattern is typical for all humans, although population differences in size exist. The pattern of growth in head circumference is similar to that of other head dimensions such as head length and width.[12] Due to the small growth velocity of head dimensions beyond the age of 3 years, studies of head growth are usually limited to the period of infancy.

Tempo of growth

In the beginning of the 20th Century, the leading American anthropologist Franz Boas had observed that "some children are throughout their childhood further along the road to maturity than others".[13,14] Indeed, individuals do not only vary in size, but also in the age at which they reach mature size, i.e. they demonstrate an individual "tempo" of growth. Other indicators of maturity (e.g. the development of secondary sex characteristics, skeletal maturation, etc.) also exhibit a variable tempo that may be different from, but is correlated with, the timing of the AGS. At the end of this chapter we will see that the sequence and relative timing of these events in adolescence is different in boys and in girls.

The main effects of variations in tempo on the shape of the human growth curve are illustrated in Fig. 4.4. The three distance and velocity curves show the growth in stature of

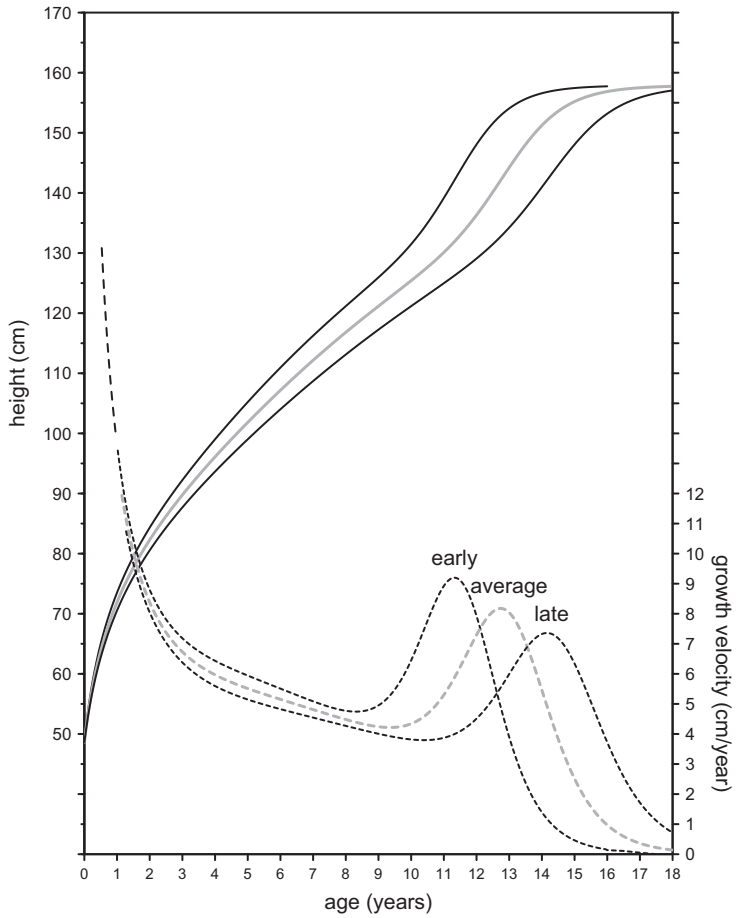

Fig. 4.4
Pattern of growth of typically early, average and late maturers: A theoretical example.

typical early, average and late maturing children who have the same size at birth and at adulthood. These three theoretical subjects have a similar growth potential illustrated by their comparable adult stature, but they differ considerably in height at each age along their growth trajectory, and consequently in the shape of their growth curve. The early maturer reaches final size at an earlier age and is taller than the average maturer throughout childhood and adolescence, while the late maturer reaches adult size at a later age and is less tall than the average maturer. The effect of differences in tempo of growth on attained height increase with age and are more apparent in periods where the slope of the growth curve is steeper such as in adolescence.

Differences in tempo thus have an impact on growth distance and velocity during childhood and adolescence, but not on final stature. Longitudinal studies have repeatedly shown that little or no correlation exists between the timing of the pubertal spurt and adult stature, i.e. early, average and late maturing children reach, on average, the same adult height.[15–20] The shorter growth cycle in early maturers is compensated for by a slightly greater growth velocity during childhood and by a more intense adolescent growth spurt. The opposite is seen in late maturing children, who have a longer childhood growth, but a less intense growth spurt. This relationship is reflected in the negative correlation between peak velocity and age at peak velocity in height.[15,21,22] This is also true for other post-cranial body dimensions,[16] but not for weight. Early maturing children tend to have, as adults, a higher weight,[13] and therefore a higher BMI.[23]

Studies on longitudinal growth of twin and family data have shown that tempo of growth is to a great extent genetically determined.[24–27] In a longitudinal study of monozygotic and dizygotic male twins, Hauspie et al.[28] found a strong genetic component in the variance of biological parameters that characterize the shape of the human growth curve, in particular the age at peak velocity, which reflects the tempo of growth. Similar findings were reported by Byard et al.[29] on the basis of familial resemblance in growth curve parameters in the Fels Longitudinal Growth Study and by Hauspie et al.[26] in Bengali children. Tanner[30] suggested that both the growth status and the tempo of growth are under genetic control, but that the genetic factors involved might be quite different. Despite the strong genetic control over tempo of growth, there is evidence that the human body can adapt to adverse environmental conditions by slowing down physical development, thus allowing a child to cope with the physiological and metabolic requirements for a balanced development. When the adverse conditions are reversed, a child usually restores its growth deficit by a period of rapid growth in order to regain its original "growth channel", the so-called "catch-up growth"[31–33] (Chapter 1). If, however, environmental stress is experienced for a long period of time or extends into the adolescent growth cycle, the resulting pattern of growth may resemble that of late maturing children. Examples of this can be found in children exposed to chronic mild undernutrition,[34] to chronic diseases such as asthma,[35] to psycho-social stress,[36–38] to

socio-economic deprivation,[39] and in children living at high altitude.[40] These conditions can lead to a small delay in reaching the adolescent growth spurt, in achieving sexual maturity, and in attaining final size. Final stature is usually not affected (i.e. is compatible with the population average) unless the long-lasting adverse conditions are severe.[33]

Growth modeling and biological parameters

Serial measurements of size, taken at regular intervals on the same subject, such as shown in Figs. 4.1–4.3, form the basis for estimating the expected growth curve of an individual (Chapter 13). Growth is generally assumed to be a smooth process when based on body measurements taken at intervals varying between several months and one year. To estimate a continuous growth curve we could linearly connect the successive measurements (as we did in Figs. 4.1–4.3), or use a smoothing technique such as splines or polynomials. These methods allow interpolation to produce a smooth curve, but they are not useful to summarize the growth curve. However, several mathematical models have been proposed to estimate a smooth continuous curve on the basis of a discrete set of measurements of growth of the same subject over time.[41–43] They all imply that the growth curve increases monotonously with age and tends toward an upper asymptote when data near adulthood are included. More than 200 models have been proposed to describe part or the whole of the human growth process,[44] but only a small number have shown to be of practical use. The possibilities and limitations of commonly used mathematical functions for analyzing human growth have been discussed by Hauspie et al.,[45] Hauspie and Chrzastek-Spruch,[46] and Hauspie and Molinari.[47] In this chapter, we will discuss the Preece Baines model I (PB1) which has been widely used to describe adolescent growth.[48] PB1 is an example of a parametric model in which the function parameters can be interpreted as biological phenomena and thus allows the study of differences between individuals and the populations to which they belong. The mathematical expression of Preece Baines Model I (PB1) is:

$$y = h_1 - \frac{2(h_1 - h_\vartheta)}{e^{s_{0(t-\vartheta)}} + e^{s_{1(t-\vartheta)}}} \tag{4.1}$$

where y is the height in cm, t the age in years, and h_1, h_θ, s_0, s_1, and θ are the five function parameters. The parameters of PB1 allow a functional interpretation of the growth curve: h_1 is the upper asymptote of the function and thus corresponds to an estimate of mature size; θ is a timing parameter that controls the location of the adolescent growth spurt along the time axis and is highly correlated with (but not exactly the same as) age at peak velocity; h_θ is the size at age θ, and parameters s_0 and s_1 are rate constants controlling respectively pre-pubertal and pubertal growth velocity. Biological parameters of the growth curve, like age at take-off (TO), age at peak height velocity (PHV), and peak height velocity itself, can be obtained with algebraic expressions that have been derived from the PB1 model.[48]

The parameters of a non-linear growth function like the PB1 curve are usually estimated with nonlinear regression analysis which minimize the squared distances between data points and the resulting curve. Algorithms for nonlinear regression analysis of user entered functions are offered by most statistical software packages.

The outcome of modeling serial growth data of an individual is a set of values for the function parameters (five in the case of PB1). Hence, individual growth modeling (or curve fitting) is a technique which summarizes longitudinal growth data in a limited number of parameters. This greatly simplifies the analysis of growth curves, by reducing the amount of data while maintaining the same information. Say a child is measured every 6 months from 2 to 18 years, which would result in 68 items of numerical information: 34 measurements of height and 34 ages. Using the PB1 model reduces these 68 items to five function parameters which relate to pre-pubertal and pubertal growth rates, age and height at take-off and peak velocity, and adult stature. This is a data reduction technique that is clearly more efficient and could be described as a "parsimonious" process. Given the volume of data that may be collected on the growth of a child, such parsimonious processes are a highly desirable first step for further analysis and interpretation of the (adolescent) growth cycle. For structural growth models like PB1, the function parameters have the same meaning for all participants and can thus be compared between individuals. By feeding the values of the function parameters into the model we can graph the smooth growth curve of an individual (Fig. 4.5). Likewise, when entering the parameter values into the first derivative of the function, we get an estimation of the instantaneous growth velocity. Velocity is defined as the change in distance over time or $(\text{height}_2 - \text{height}_1)/(\text{age}_2 - \text{age}_1)$ and is thus the "first derivative" of distance. Likewise, the second derivative would be acceleration, or change in velocity over time. The formula for the growth velocity of a PB1 model is given in Eq. (4.2):

$$y' = \frac{2(h_1 - h_\vartheta)\left(s_0 e^{s_0(t-\vartheta)} + s_1 e^{s_1(t-\vartheta)}\right)}{\left(e^{s_0(t-\vartheta)} + e^{s_1(t-\vartheta)}\right)} \tag{4.2}$$

The distance curve in Fig. 4.5 shows the PB1 function fitted to the observed height measurements plotted in Fig. 4.1. The lower part of Fig. 4.5 is a plot of the yearly increments obtained by differencing the data, together with the instantaneous velocity curve obtained as the mathematical first derivative of the fitted distance curve. The corresponding values of the function parameters and derived biological parameters are listed in Table 4.1. The location of some of these parameters is also indicated on the curves in Fig. 4.5.

The precision of the fit of a nonlinear model is given by the standard error of estimate (SEE), also called the residual standard deviation (RSD), or root mean square error

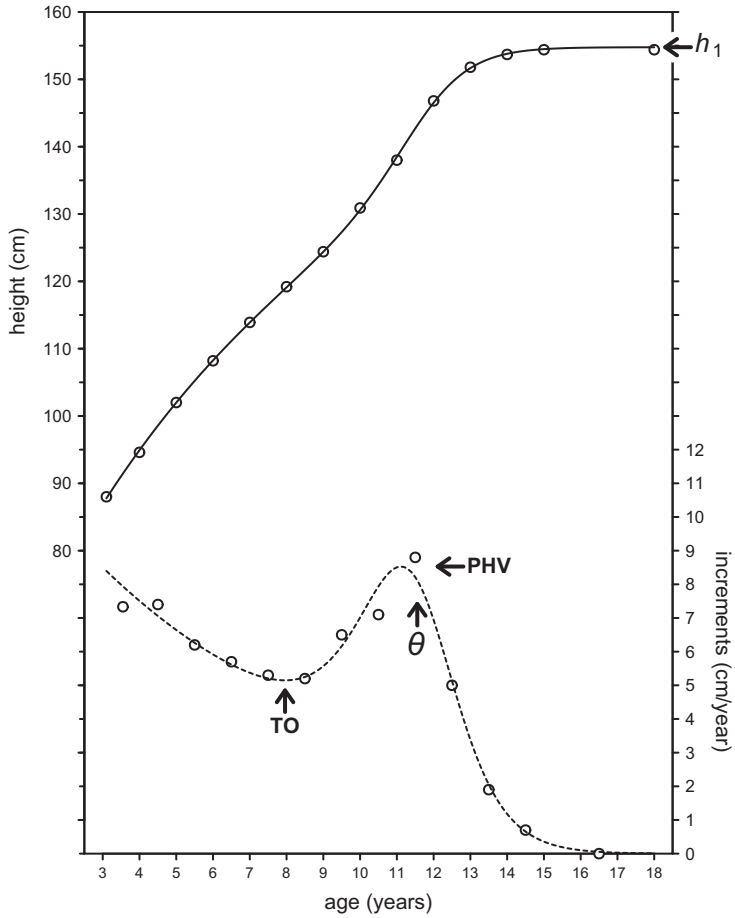

Fig. 4.5

Growth in height of a Belgian girl between 3 and 18 years of age. The upper part shows a plot of the height-for-age data together with the Preece-Baines model 1, while the lower part shows the yearly increments in weight with the first derivative of the fitted curve. (Girl No. 29 from the Belgian Growth Study of the Normal Child[1–3]).

(RMSE). The RSD is the square root of the sum of the squared residuals divided by the degrees of freedom of the model (Eq. 4.3):

$$RSD = \sqrt{\frac{\sum_{i=1}^{n}\left(y_i - \hat{y}\right)^2}{n-k}} \tag{4.3}$$

where y_i is the actual measured height at age t_i, $\hat{y}_i$ the height at age t_i predicted from the model fit, $(y_i - \hat{y}_i)$ is the residual, n the number of height measurements, and k the number of parameters in the model (five in the case of PB1). (To all intents and purposes this is an

Table 4.1: Function parameters, model fit and biological parameters obtained by fitting Preece Baines model 1 to the height data of Girl No. 29 from the Belgian Growth Study of the Normal Child [1–3].

h_1	154.4 cm
h_0	143.7 cm
s_0	0.1374
s_1	1.450
θ	11.63 years
Residual variance	0.144 cm^2
Residual standard deviation	0.380 cm
Age at take-off	8.33 years
Height at take-off	121.2 cm
Velocity at take-off	5.1 cm/year
Age at peak velocity	11.18 years
Height at peak velocity	139.8 cm
Velocity at peak velocity	8.9 cm/year
Adolescent gain	33.2 cm

average deviation – the deviations are squared to get rid of negative values, divided by the degrees of freedom, and square-rooted to transpose back to the unsquared value.) It is generally accepted that the growth curve is adequately fitted if the SEE is of the same order as the measurement error of the trait under consideration. Measurement error is calculated from a test-retest analysis of, in this case, height measurements and is the standard deviation of the differences between repeated measurements (see Chapter 11). Typically, this is about 0.5 cm for stature during childhood and adolescence. A systematic departure of the data from the function (bias) can be detected with the runs test,[49] and with an analysis of autocorrelation in the model residuals. Autocorrelation occurs when consecutive measurements are located on the same side of the curve and are thus systematically under- or overestimated. This points to a deficiency of the model to describe local patterns that are observed in the data.

Large values of the RSD, and systematic bias, generally originate from low precision data, or from an inappropriate choice of growth model. Low-precision data are observations that were recorded with a large measurement error, due to inexperienced measurers, large inter-measurer variation, or the use of inadequate measuring techniques or devices. The choice for an appropriate structural growth model depends on the age range under study and the expected shape of the growth curve. The PB1 model was originally designed to study adolescent growth and is not suitable to model growth during infancy or early childhood. Whenever longitudinal data from birth are at hand, other models such as the triple logistic function[50] or the JPA-2 function[51] are better alternatives. Likewise, functions such as the Count or Jenss-Bayley growth curve models are more suitable when the data only cover the period before the AGS.[47] Structural or parametric models explicitly assume

a specific shape of the growth curve that includes particular features (such as a growth spurt). The fitted curve will always show these features, sometimes prominent, sometimes not, even when not present in the data. The PB1 model was designed for post-cranial skeletal dimension and assumes a pubertal spurt with a local minimum in growth velocity at take-off. It is therefore inappropriate for growth in weight, which has a pubertal spurt, but no minimum velocity at take-off. Moreover, weight does not *per se* increase monotonously with age, and may show a growth pattern that is not compatible with a structural model. The PB1 model is also inappropriate for describing the growth in head circumference, because of the lack of pubertal spurt in this trait. Features that are not structurally incorporated in the model will never be visible in the resulting growth curve, even when clearly present in the data. Examples are mid-childhood growth spurts or unusual variations of the growth rate under certain pathological conditions.

One should also be suspicious about estimations of final size by structural growth models when the observed data points do not give a clear indication that the end of the growth phase is near. For instance, estimates of final height, typically at a velocity of less than 1 cm/year, are fairly unreliable if the last observed increment exceeds 2 cm/year. Least-squares techniques are weak in fitting parameters beyond the observation range and thus inappropriate to extrapolate beyond the known data. Analogous problems may arise when the lower bound of the age range does not include the take-off of the adolescent growth spurt in the case of PB1. In such a situation the estimation of the age at take-off and all derived biological parameters by a PB1 fit is not under control of the data and likely to be erroneous. A possible solution to the problem of extrapolation when data at the upper or lower boundary are missing, is the use of a Bayesian approach which relies on prior knowledge about the shape of the growth curve instead of least-squares techniques for parameter estimation.[50,52]

Growth variables that do not necessarily have a monotonously increasing pattern (such as weight, body mass index, skinfolds) cannot be successfully described by structural models such as non-linear growth functions. Non-structural approaches, such as polynomials, smoothing splines and kernel estimation are more appropriate for these kind of traits.[15,53]

Besides producing a smooth continuous curve for growth and growth velocity, and summarizing the growth data, one of the main goals of mathematical modeling of human growth data is to estimate milestones of the growth process of an individual (biological parameters), such as age, size, and velocity at take-off and at peak velocity (Table 4.1). Biological parameters, obtained by fitting a growth model, characterize the shape of the human growth curve and form a basis for studies of genetic and environmental factors that control the dynamics of human growth. On the population level, these growth models can also be used to estimate the "typical average" curve using the mean of each constant to derive the "mean-constant curve".

Individual versus average growth

Our knowledge of the shape of the growth curve comes from longitudinal studies, i.e. based on series of growth measurements of the same participants over time, which allows the determination of part or the whole of the individual growth process. However, the majority of growth studies are cross-sectional, i.e. based on single measurements taken from individuals who differ in age. Cross-sectional growth data allow an estimate of the central tendency and variation of anthropometric variables at each age in a population, and to construct smooth centile lines showing the "average" and the limits of "normal" variation of a particular trait in that population. These centile lines form the basis of most growth reference curves (Chapters 13 and 14). Despite the immense merits of cross-sectional growth surveys in constructing growth reference charts, and in epidemiological studies of genetic and environmental factors involved in growth, they only give a static picture of the population variation in growth at different ages and are hopelessly weak in providing information on the dynamics of individual growth patterns over time.

In adolescence, differences in tempo are very pronounced. In early adolescent ages, some individuals will be growing at peak height velocity while others still have to start their growth spurt. In mid-adolescence, early maturers will approach final height (with their growth velocity nearing zero), while others grow at maximum velocity. A consequence of these variations in tempo is that a cross-sectional mean curve, to some extent, smooths out the adolescent growth spurt. This effect is illustrated in Fig. 4.6, based on the longitudinal growth curves of two boys taken from the Lublin Longitudinal Growth Study.[54] Both subjects differ in the timing of their adolescent growth spurt, with a maximum increment in height that occurs at respectively 12.5 and 14.5 years of age. By taking the average height at each age, effectively ignoring the difference in timing of the adolescent growth spurt in both participants, we end up with a cross-sectional mean curve that shows a longer but less intense growth spurt. This is reflected in the less steep slope of the mean distance curve, but the effect is even more striking when the yearly increments in height of both participants are compared with the cross-sectional average of these increments. Both boys have a clear adolescent spurt with a maximum increment in height of respectively 9.9 and 7.8 cm/year, while the cross-sectional mean of the increments has a peak that is lower, and a "spurt" that lasts longer compared to the individual curves. This phenomenon is called the "phase-difference" effect.[9]

The example given in Fig. 4.6 illustrates how the pattern of growth of an individual differs from a cross-sectional mean growth curve, especially during adolescence. Although this example is based on averaging two longitudinal growth curves, exactly the same mechanism applies to the means in cross-sectional data, and to the means in longitudinal data when not accounting for differences in tempo. It is the main reason why growth records of an individual over time do not match any of the centile lines shown by cross-

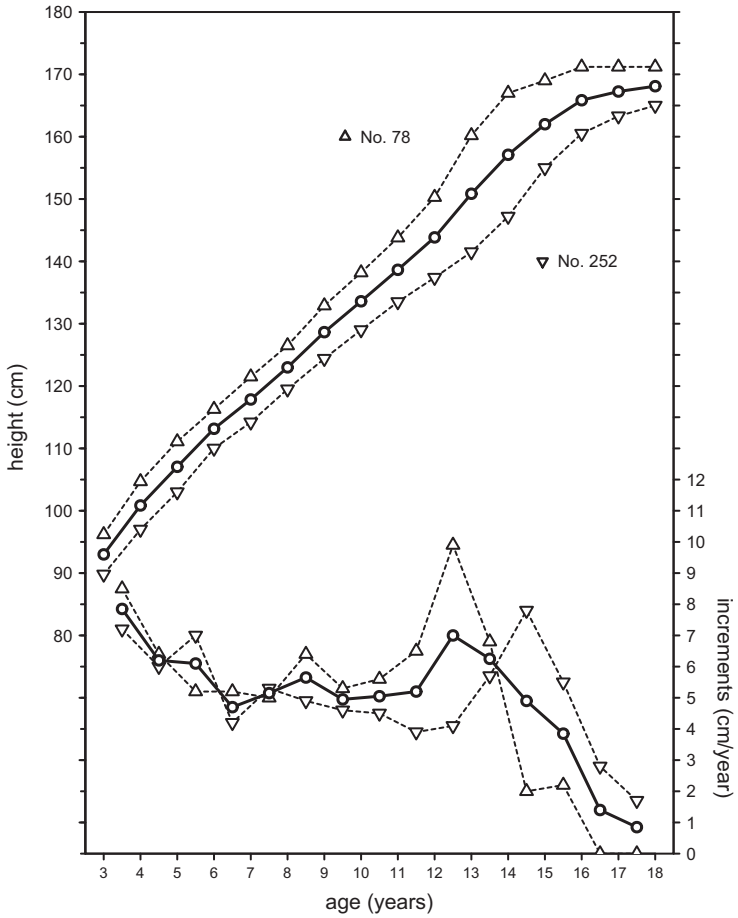

Fig. 4.6
Distance and velocity curves of two Polish boys (open markers) with the cross sectional mean curve (filled markers). Average velocities also correspond to increments of the average distance curve. *Source: Data from the Lublin Longitudinal Growth Study*[54].

sectional growth charts (even when based on longitudinal data) and why these charts are not useful to evaluate the normality of the *pattern* of growth over time. This type of growth chart is said to be *unconditioned for tempo*.

The difference between individual and average growth was recognized a long time ago (by Boas in 1892, and by Shuttleworth in 1937; see Tanner[14]), but it was not until the mid 1960's that Tanner et al.[9,10] introduced *tempo-conditioned* growth standards for height, weight, height velocity and weight velocity, based on longitudinal data of British children. These standards not only show the classical cross-sectional centile distribution for attained size, and velocity at each age, but also the "normal" variation in the *shape* of the growth

curve. The references for shape were based on an analysis of longitudinal data after centering each individual growth curve around the average age at peak velocity. Chronological age is thus replaced with age corrected for tempo, hence *tempo-conditioned* standards.

Fig. 4.7A illustrates the effect of this approach on the mean height velocity curves of the two Polish boys from Fig. 4.6. When taking averages of height velocity (or height distance), after centering the velocity curves at the mean age at peak height velocity, we obtain a mean velocity curve which can be considered as representative for both individuals, i.e. with an age at peak velocity and a peak velocity that is the average of

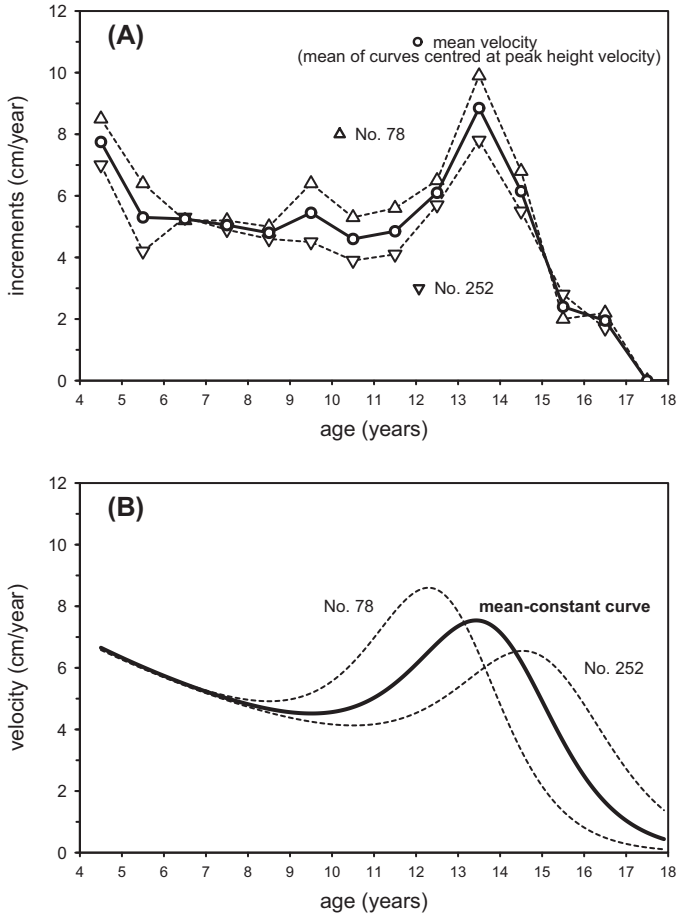

Fig. 4.7

(A) Yearly increments in height of two Polish boys, centered on the average age at peak height velocity (open markers) and cross-sectional means of the peak velocity centered curves (filled markers); and (B) PB1 velocity curves of these boys with the mean-constant curve. *Source: Data from the Lublin Longitudinal Growth Study*[54].

both subjects. Subsequently Tanner and Davies[6] used the same principle to produce clinical longitudinal standards for height and height velocity in North American children. Wachholder[2] and Hauspie[3] achieved the same goal with a technique based on curve fitting, to produce clinical standards for growth and growth velocity in Belgian children. They estimated the typical average pattern of growth with "mean-constant" curves. A mean-constant curve for adolescent growth is obtained by fitting the Preece-Baines model 1 to each individual in a sample and by feeding the mean values of the function parameters into the model. The resulting curve represents the average growth pattern in the population, i.e. with a peak velocity and an age at peak velocity which is characteristic or typical for the group.[42] The PB1 velocity curves of the two Polish boys are shown together with their mean-constant curve in Fig. 4.7B. The result is very much alike that of the peak velocity centered curves. Note however that the PB1 curve slightly underestimates peak velocity, a known minor weakness of the PB1 model.[46]

Sex differences in growth

It is well known that adult females are on the average smaller than adult males for most linear body dimensions, in particular height, sitting height and leg length.[13,55] Although some differences between boys and girls are already observed at birth, they remain generally small until the early teens, when the girls start their pubertal growth spurt. Because of the two-year difference in age of onset of the adolescent spurt, 11 to 13-year old European girls are, on average, taller and heavier than boys of the same age.[56] Some studies suggest that the magnitude of sex differences in a population depends on the average size in adults.[57,58] However, Eveleth[59] found a relatively large sex difference in adult stature in Amerindians, a population that has a relatively small adult size. Similar findings were reported in India.[55] Eveleth postulated that genetic factors probably play an important role in establishing both the mature size and sex differences, but it is also conceivable that in certain societies boys are more favourably treated, which allows them to better express their genetic growth potential.

Sex differences in growth during infancy, childhood, and adulthood, as well as the points of intersection between the male and female average growth curves can be derived from cross-sectional data in a relatively accurate way. However, for reasons explained above, a study of the manner in which sex differences in size arise during the growth process depends on the availability of longitudinal data and the use of appropriate analytical methods.[21] A particularly suitable approach to analyze the dynamics of sexual dimorphism in human growth is to compare the typical average male and female curve in a population, estimated with a mean-constant curve. As an example, the average growth (mean-constant curve) of Belgian boys and girls is shown in Fig. 4.8. We consider the total pre-pubertal growth as the size achieved up to the age at take-off, and adolescent growth (or adolescent

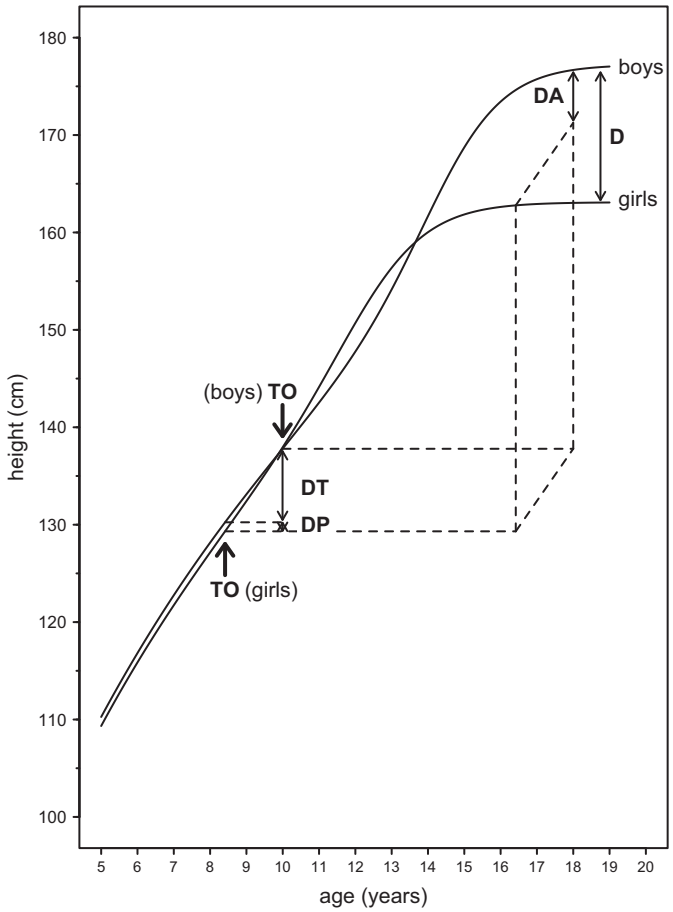

Fig. 4.8

Decomposition of sex differences in adult stature (D) into three additive components: differences at take-off in girls (DP), growth in boys between take-off in girls and take-off in boys (DT), and difference in adolescent gain (DA).

gain) as the amount of growth between take-off and adulthood. Fig. 4.8 illustrates how the sex difference in adult size (D) can be expressed as the sum of three additive components, $D = DP + DT + DA$, where DA is the difference in adolescent gain between boys and girls; DP the difference in size at take-off in girls; and DT the amount of growth achieved by the boys between take-off in girls and take-off in boys. DT corresponds to the longer childhood growth that is observed in boys, and DP + DT to the difference in total prepubertal growth between both sexes. Using this technique, Hauspie et al.[55] analyzed the origin of sex differences in height, sitting height, shoulder width and hip width in British children. The results are summarized in Table 4.2.

Table 4.2: Decomposition of sexual dimorphism in adult size of height, sitting height, shoulder width and hip width in British children into three additive components.[55]

	Height (cm)	Sitting height (cm)	Shoulder width (cm)	Hip width (cm)
Total difference (D):	12.0	4.5	3.7	−0.6
Difference at take-off in girls (DP):	2.1	0.3	0.3	−0.1
Growth in boys between take-off in girls and take-off in boys (DT):	7.9	3.5	1.7	1.5
Difference in adolescent gain (DA):	2.0	0.7	1.7	−2.0

The largest contribution to the 12.0 cm sex difference in adult height comes from the later onset of the adolescent growth spurt (or longer childhood growth) in boys (DT = 7.9 cm). Sex differences in pre-adolescent growth (DA = 2.0 cm) and in adolescent gain (2.1 cm) are significantly smaller. The proportional contribution of each of these components may be slightly different in other populations. In West Bengal, sex difference in adult height is larger (D = 14.2 cm), mainly due to a more important adolescent gain,[59] but in the Belgian population, the contribution of DT to the sex differences in adult height was comparable to that observed in UK children.[60] The decomposition of the adult sex difference in sitting height is proportional to that of stature, but the adolescent gain in shoulder width is relatively larger in boys than in girls. Adult sex differences in hip width are almost negligible, because the longer childhood growth of 1.5 cm in boys is compensated by a greater adolescent gain in hip width (2.0 cm) in girls (Table 4.2). For all these body dimensions, differences before take-off in girls are small. In conclusion, a comparison of average growth in boys and girls shows that the differences in linear body dimensions that are observed in adults, emerge during adolescence. Within the adolescent period, a longer childhood growth in boys can be identified as an important contributor to these differences.

Similar sex differences in tempo exist for other markers of maturation. The timing of these events relative to the AGS is however different for boys and girls. Fig. 4.9 shows the sequence of events at puberty based on a longitudinal study of children in the UK by Marshall and Tanner.[61,62] In girls, the AGS is a relative early event and take-off may well be the first sign of puberty onset, while take-off in boys usually follows the appearance of the first signs of sexual maturation.

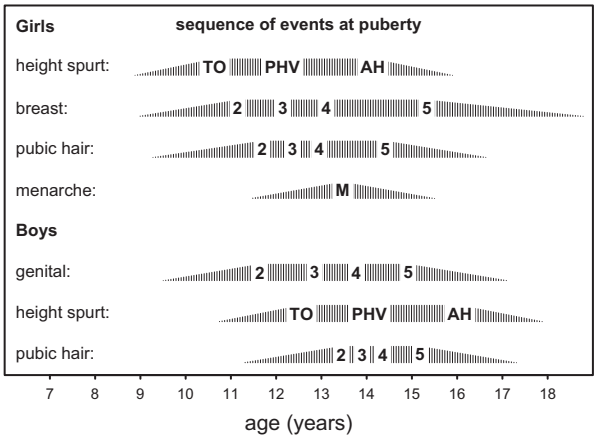

Fig. 4.9

Sequence of events at puberty in boys and girls based on a longitudinal study of children in the UK.[61,62] The adolescent growth spurt a relative early event in girls and a relative late event in boys. The age scale shows the timing of events in an average boy and girl, but the range of ages that may be observed is also indicated.

Summary

Growth at adolescence is characterized by the presence of a growth spurt in height and weight, but not in head circumference. Several milestones of adolescent growth can be identified on the distance and velocity curves. The adolescent growth spurt (AGS) starts at take-off, and ends when final size is reached. The period of maximum growth is denoted as peak velocity. The timing and magnitude of the AGS is highly variable, due to which large transient differences in size may occur between individuals of the same chronological age. Differences in tempo of growth have however no impact on final height. Most of our knowledge on the shape of the growth curve comes from longitudinal studies, in which serial measurements in the same individual are often analyzed with the help of mathematical growth models. These models allow us to summarize the growth curve in a limited number of constants, and to identify important milestones and biological parameters that characterize the pattern of growth. The Preece-Baines model 1 is an example of a structural model that is particularly useful for adolescent growth in height. The majority of growth studies are however based on cross-sectional data. As a consequence of variations in tempo of growth, a cross-sectional mean curve will show a longer but less intense growth spurt, when compared to the growth curve of an individual. It is therefore not representative for the pattern of growth of individual children. Methods that account for individual differences in timing and magnitude of peak velocity, include centering the individual growth curves around the average age at peak velocity when analyzing the data graphically, and the mean-constant curve when using growth models. Finally, differences in linear body dimensions that are observed between adult males and

females, emerge during adolescence. Within the adolescent period, the longer childhood growth in boys is an important contributor to the sexual dimorphism in final height.

Suggested reading

Many papers and textbooks give a concise description of the pattern of human growth. When querying databases and repositories, be sure to look for papers based on longitudinal data and exploiting the longitudinal nature of the data by using appropriate analytical methods. Tempo of growth is discussed in Tanner et al.[9,10] A review of various growth models and curve fitting techniques is given in Hauspie and Molinari[47] and in Chapter 13. Tanner et al.[9,10] is a citation classic that describes the graphical method to account for individual differences in growth, while Hauspie and Wachholder[3] demonstrate the use of a mean-constant curve. The decomposition of sexual dimorphism in height is based on Hauspie et al.[55] and Koziel et al.[60]

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CHAPTER 5

Puberty

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Puberty, the transition from an immature to a reproductively mature state, is a neuroendocrine process with broad ramifications for anatomy and physiology. In humans, puberty is a consequence of the reactivation of pulsatile gonadotropin-releasing hormone (GnRH) secretion by the hypothalamus. Upstream inputs to the GnRH-secreting neurons are regulated by other peptides and neuromodulators, including kisspeptin, neuropeptide Y, glutamate, gamma-aminobutyrate and neurokinin B. These inputs modify the timing of puberty in response to factors such as energy balance and psychosocial stress. Downstream consequences of the reactivation of pulsatile GnRH secretion include progressive increases in pulsatile gonadotropin secretion by the pituitary gland and the initiation of gametogenesis and hormone production by the gonads. Increasing levels of circulating sex steroids lead to the maturation of other reproductive tract organs and female breast development, the pubertal growth spurt, and the development of secondary sexual characteristics, among many other aspects of adult morphology and physiology.

Introduction

Puberty refers to the onset of adult reproductive capacity. As a milestone in human development, puberty is quite dramatic, involving a rapid transformation of anatomy, physiology and behavior. Other than pregnancy, it is probably the most abrupt and encompassing developmental transition that human beings undergo between birth and death. It is also a transition of deep cultural significance in most societies around the world, often marked by special rituals and ceremonies.[1]

As dramatic as it is, however, puberty is not really an instantaneous event or a discrete state, but a process that is integrated more or less smoothly with the antecedent and consequent developmental phases of immaturity and adulthood. At its core, puberty is a neuroendocrine transformation in the processes that regulate reproductive physiology. This transformation arises, however, from physiological mechanisms that are already latent in the prepubertal child, and it initiates a trajectory of change that merges smoothly with other age-dependent changes that continue through adult life. The Rubicon that is crossed

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in this process is the frontier of reproductive capability. Before puberty, people are not capable of producing offspring, however capable they might otherwise be. After puberty, people are capable of producing offspring, regardless of how much growth has yet to take place in their other skills and capacities. Puberty is distinct from adolescence, as the word is commonly used, because it does not take into account the social and legal privileges and obligations that accompany the transition from juvenility to adulthood in most societies. Its focus is purely on the ability to procreate.

The physiological processes that guide and regulate this pivotal transformation from child into adult have been foci of research for decades, and a great deal of progress has been made in elucidating many of the details. This progress has led to innovative treatments for pathologies of pubertal development, as well as new formulations of the evolution of human life history. But many mysteries and controversies remain. The purpose of this chapter is to introduce students to the current state of knowledge about, and research into, the physiology of human puberty and its relationship to other aspects of human growth and development. The presentation will necessarily be incomplete and will focus on those aspects that the authors think are most important. However, it is also hoped that the chapter will prepare students for further pursuing those issues that may interest them.

The presentation will have three main sections. "The neuroendocrinology of puberty" provides a brief sketch of the hormonal axis that controls reproductive physiology, and the pulsatile nature of hypothalamic secretion of gonadotropin-releasing hormone (GnRH) is described. Then the development of GnRH secretion and its central role in puberty is reviewed, and finally some of the major central nervous system controls of GnRH secretion are discussed. At the end of this section, readers should be able to answer the questions: How does the hypothalamic–pituitary–gonadal (HPG) axis control puberty? What initiates mature HPG axis function?

"Upstream factors influencing pubertal timing" discusses some of the major factors that influence the timing of neuroendocrinological activation at puberty, focusing on genetics, energetics and psychosocial factors. The reader may approach this section with the question: Why is the timing of puberty variable across individuals?

"Downstream consequences of pubertal activation of the hypothalamic–pituitary–gonadal axis" will describe how the activation of the neuroendocrine reproductive axis affects the rest of the body, including the pubertal growth spurt, the development of secondary sexual characteristics and changes in behavior. This section addresses the question: What are the effects of HPG axis activation?

The chapter closes by offering a provisional framework for organizing what is known about human puberty and its timing. In order to describe the function of individual

components of the HPG axis, this section will examine, among other evidence, research in animal models, particularly mammals with neuroendocrine function similar to that in humans. In animal models, researchers can experimentally manipulate hormones, components of neural anatomy, gene expression and gonadal function, which is not possible to do systematically or ethically in humans. This evidence allows the function of different organs, hormones and genes to be isolated. In addition, cases of naturally occurring pathology in humans are presented to make inferences about the typical function of receptors, enzymes and organs from the consequences of their malfunction.

A note on sex and gender terminology: Not all people with female-assigned anatomy identify as female and not all people with male-assigned anatomy identify as male. It is also the case that people's chromosomes, gonads, and genitalia may differ from one another in biological sex, e.g. a person may be born with an X-and a Y-chromosome, undescended testes, and a vulva. This chapter, for the sake of simplicity, assumes consistent genetic, gonadal, and genital sex within individuals. "Female" refers to people with two X chromosomes, ovaries, a uterus, and a vagina, while "male" refers to people with an X and a Y chromosome, testes, and a penis. For information on pubertal development among intersex individuals and people with disorders of sexual development, and on changing the neuroendocrine course of puberty to affirm gender, please see resources in the references.[158–160]

The material in this chapter is challenging in two ways. First, it characterizes a wide array of integrated neurological, endocrinological and auxological processes. The reader may wish to organize this material by asking: How does each process contribute to adult reproductive function? Second, the authors have tried to present the major points together with enough supporting detail to make the system comprehensible to general students of human growth and development. Therefore, many details of endocrinology and neurobiology that are necessary to a fuller understanding of reproductive and pubertal physiology may be omitted. It is hoped that the material in this chapter will prepare interested students for pursuing a deeper understanding using some of the suggested references.

The neuroendocrinology of puberty

Puberty has its own specific neuroendocrinology, which we will now examine.

Interactions of the endocrine and nervous systems

The endocrine system is one of three major regulatory systems in the body, the two others being the nervous system and the immune system. All three systems utilize chemical messenger molecules to communicate between cells. These molecules interact with

specific receptor molecules either on the surface or in the interior of target cells. In the nervous system, the messenger molecules are called neurotransmitters or neuromodulators and ordinarily carry information between immediately adjacent neurons across a tiny synaptic cleft, measured in angstroms. In the endocrine system, the messenger molecules are called hormones and ordinarily carry information through the bloodstream from a site of origin to many dispersed target cells, over distances measured in millimeters to meters. One important exception to these two "ordinary" scenarios that have features of each of them is the secretion of a messenger molecule by a neuron into the blood. When this occurs, it is referred to as neuroendocrine secretion. The molecule is produced at the axon terminal of a neuron, like a neurotransmitter, but it is transmitted through the bloodstream, like a hormone.

The hypothalamic–pituitary–gonadal axis

It is important to understand the mechanisms of interaction between the nervous and endocrine systems because reproduction in humans and other mammals is hormonally controlled by a set of three interacting parts: the hypothalamus of the brain, the pituitary gland suspended at the base of the brain, and the gonads (ovaries in the female, testes in the male), which are endocrine organs. As a unit, the hypothalamus, pituitary, and gonads are referred to as the hypothalamic–pituitary–gonadal (HPG) axis. Hormonal signals are passed between the components of this axis and other parts of the body in maturing humans of all sexes. The HPG axis is active in fetal life and again in early infancy, but is only minimally active during childhood.[2,3,161] The central feature of puberty is now understood as the reactivation the HPG axis after the quiescence of childhood. All the other aspects of puberty, the various transformations of anatomy, physiology and behavior that are externally evident, are downstream consequences of this central, neuroendocrine event.

An understanding of human puberty, therefore, begins with an understanding of the HPG axis and its developmental trajectory. This section will provide a quick sketch of the HPG axis, forgoing much of the detail that would be necessary to understand the full regulation of adult reproduction.

The hypothalamus is a region at the base of the brain where the two hemispheres of the neocortex meet below the third ventricle. The hypothalamus is composed of several separate clusters of cell bodies known as nuclei. These hypothalamic nuclei control a number of different autonomic functions, including the regulation of blood osmolality, circadian rhythms, core body temperature and many others, including reproduction. Inputs to the hypothalamus arrive from many other brain regions, including the limbic system and the cortex. Outputs from the hypothalamus go primarily to the two parts of the pituitary gland.

The pituitary gland is a small organ consisting of two different tissues sitting directly under the hypothalamus in a bony capsule known as the sella turçica. The anterior pituitary is composed of glandular tissue embryologically derived from the roof of the pharynx. It is connected to the hypothalamus by an extremely small vascular connection known as the hypophyseal portal system. This small set of blood vessels has capillary beds both in the hypothalamus and in the anterior pituitary, extends only a few millimeters and contains only about a milliliter of blood. Axons from cell bodies in the hypothalamus terminate in the capillary bed at the hypothalamic end of the hypophyseal portal system.

The posterior pituitary gland is embryologically derived from the same tissue as the hypothalamus and remains physically connected to it by the pituitary stalk. Axons from cell bodies in the hypothalamus extend into the posterior pituitary with terminal buds on the capillaries that supply blood to that part of the gland.

The anterior and posterior pituitary glands differ not only ontogenetically but also functionally. Neuroendocrine products of the hypothalamus, or releasing hormones, enter the hypophyseal portal system of the anterior pituitary and stimulate release of the anterior pituitary's own endocrine products. In contrast, the posterior pituitary stores neurohormones produced in the hypothalamus itself and releases them directly into circulation. The rest of this discussion of HPG axis function in puberty will focus only on the role of the anterior pituitary.

The gonads are the sites of gamete production in both sexes. They are also important endocrine glands, producing steroid and protein hormones. The ovaries of the female are located in the coelomic cavity of the lower abdomen connected by the broad ligament to the fallopian tubes and uterus. The testes of the male are located in the external scrotal sac.

Each part of the HPG axis secretes specific hormones. The hypothalamus secretes a small peptide hormone commonly known as gonadotropin-releasing hormone (GnRH) (but sometimes referred to as luteinizing hormone-releasing hormone). GnRH is secreted by a diffuse network of less than 2000 neurons located in the mediobasal hypothalamus.[4] Secretion from the axon terminals of these neurons occurs directly into the hypophyseal portal system through which GnRH is carried to the anterior pituitary. GnRH is produced in extremely low amounts and is measurable only in the hypophyseal portal system itself. Once in the systemic circulation the levels become too dilute to measure accurately, and the molecule itself is soon degraded. These facts impose severe limitations on direct observations of GnRH in vivo.

In response to hypothalamic GnRH, the anterior pituitary secretes two protein hormones into the systemic circulation: follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These hormones, together known as gonadotropins, travel to the gonads where they

stimulate gamete production and hormone secretion. Testes produce two particularly important hormones: testosterone (a steroid) and inhibin (a protein). Ovaries produce two steroids, estradiol and progesterone, the latter only during the second half of an ovarian cycle after ovulation and during pregnancy. Ovaries also produce inhibin.

Gonadal steroids have potent effects throughout the body, including effects on reproductive organs, body composition and behavior. They also have effects on the hypothalamus and anterior pituitary. Inhibin in both sexes functions to provide feedback control on pituitary activity. In males, these feedback effects generally serve to sustain constant sperm production and to maintain testosterone levels in a broad normal range. In females, the feedback of gonadal steroids and inhibin serves to coordinate monthly waves of gamete maturation and menstrual bleeding. The signals not only control the immediate reproductive cycle but also mediate gamete maturation for future cycles.[162]

At first encounter, the student may find the HPG axis unnecessarily complex. Why so many parts and so many hormones? It may help to think of the axis primarily in terms of its two ends: the brain and the gonads. The gonads are the sites of gamete production, clearly essential for reproduction. The brain is the place where all kinds of information about the organism and its environment are integrated, including information that may indicate when conditions (both internal and external) are best for reproduction. The information gathered by the brain can ultimately affect GnRH production by the hypothalamus and thus be passed through the pituitary to the gonads. The pituitary in essence amplifies the tiny neural signal generated by the hypothalamus into a larger, longer lasting hormonal signal that can be received by the gonads.

But why, one might ask, do the gonads secrete hormones in addition to producing gametes? Couldn't the gonads and the rest of the reproductive organs simply respond to the hypothalamic signals relayed through the pituitary? One important part of the answer is that the steroid hormones secreted by the gonads help to coordinate many other aspects of anatomy, physiology and behavior that are important for successful reproduction. They influence the way energy is metabolized and allocated in order to support reproduction in both sexes. They mediate the growth processes that cause individuals to reach adult size and the degree of sexual dimorphism in both the skeleton and soft tissues. They also influence and coordinate reproductive behavior, integrating environmental information with physiology. These functions are particularly evident in many seasonally breeding mammals, deer for instance, where steroids control changes in body composition and antler growth, as well as mating behavior. But similar functions are served, more or less conspicuously, in all mammals.

Thus, the HPG axis can be viewed as the control center for reproduction, where multiple sources of information are integrated and resulting control signals passed on to the gonads. The gonads both produce the gametes that will potentially form a new organism and send

signals throughout the body to coordinate changes in anatomy, physiology and behavior, all geared toward securing reproductive success.

Pulsatile gonadotropin-releasing hormone secretion

Gonadal and pituitary hormones can be readily measured in various bodily fluids using modern techniques. GnRH, on the other hand, can only be measured in samples of blood taken directly from the hypophyseal portal system. In the 1980s, Knobil and his colleagues published a set of landmark studies based on sampling blood from this tiny portal system in restrained rhesus monkeys.[5-7] They showed that, in adult monkeys, GnRH is secreted in regular pulses slightly more than an hour apart. Subsequent studies demonstrated that, in monkeys where the hypothalamus was surgically ablated, exogenous administration of GnRH at a pulse rate of once every 60–90 min resulted in normal gonadotropin secretion and normal gonadal function.[8] If the pulse rate was slower or faster, however, gonadotropin secretion was interrupted and gonadal function would eventually stop.[9] They also demonstrated that if a regular, pulsatile pattern of GnRH was administered to an immature female rhesus monkey the monkey would experience puberty and begin normal adult ovarian cycling.[10] Similar results were later obtained for male rhesus monkeys by Plant and colleagues.[2]

Similar experiments are, of course, not possible in humans. However, the knowledge obtained from the monkey experiments has led to effective treatments for various pathological syndromes of precocious and delayed puberty in humans. For example, Kallman's syndrome results from a failure of the GnRH secreting neurons to properly migrate into the hypothalamus during embryogenesis. Affected individuals have no endogenous secretion of GnRH and do not spontaneously go through puberty. However, if GnRH is administered exogenously in 60–90 min pulses via an intravenous pump system, normal pubertal maturation can be induced. Notably, varying the pulse rate above or below the 60–90 min frequency interrupts pituitary and gonadal function, just as in the rhesus monkeys.[11]

Variants of GnRH have been synthesized that have much longer half-lives in the blood than the native peptide. Administering these synthetic variants can swamp the normal pulsatile GnRH signal received by the pituitary and instead provide a chronic, non-pulsatile signal. The result is a shutdown of the HPG axis. Administration of these compounds is now used to halt pubertal maturation in various cases of precocious puberty in humans. When the affected individual reaches an appropriate age, the administration of the synthetic compounds can stop and natural GnRH secretion be allowed once again to stimulate pituitary and gonadal function.[12,13] The same compounds can arrest HPG activity in adults and suppress gonadotropin production in postmenopausal women, women suffering from estrogen-sensitive cancers, and men with prostate cancer.[14–16,163]

Studies such as these have established the role of 60–90 min pulsatile GnRH as an obligate condition for secretion of adult levels of gonadotropins and gonadal steroids. Pulsatile GnRH secretion plays the role of an "on/off" switch for the rest of the axis. All other aspects of axis function, including regular ovarian cycling in females, are controlled by feedback from gonadal hormones and do not depend on any variation in GnRH secretory pattern.

Reactivation of pulsatile gonadotropin-releasing hormone secretion

GnRH-secreting neurons arise from the olfactory placode and migrate into position early in embryogenesis.[17,18] They appear to have an innate capacity for pulsatile GnRH secretion and will continue this pattern even when maintained in vitro.[19–21] The pulsatile pattern of secretion is apparently active even as the neurons are completing their embryonic migration, resulting in the in utero activation of the HPG axis.[22] Negative feedback of placental steroids holds fetal pituitary and gonadal activity in check during the latter part of gestation until the withdrawal of placental steroids at birth leads to a second postnatal activation of the axis. Pituitary and gonadal activity recede to low baseline levels, however, during the first years of life. At puberty, the HPG axis is reactivated once more, leading to adult levels of circulating gonadotropins and gonadal steroids.[3,23,161]

The pattern of infant and childhood suppression of gonadotropin secretion and reactivation a decade or more later has been observed in people with gonadal dysgenesis (failure of gonadal development) and thus does not appear to be dependent on feedback of gonadal steroids or inhibin.[24] A similar pattern has been observed in gonadectomized rhesus monkeys.[25,26] In animal models, the *GnRH-1* gene is expressed at high levels prior to puberty and GnRH production occurs at adult levels.[27–29] Only the pulsatile pattern of GnRH secretion is lacking. The resumption of this pulsatile pattern results from both a reduction in inhibitory transsynaptic inputs and an increase in excitatory transsynaptic and glial inputs.[164] There appears to be no single, proximate signal that determines the timing of reinitiation of pulsatile GnRH secretion at puberty. Information about growth and metabolism are integrated in a species-specific manner, modified by individual genetic variation.

Proximate regulation of gonadotropin-releasing hormone secretion

The small population of GnRH-secreting neurons serves as the integrating center for a wide variety of inputs to the control of mammalian reproduction.[2] Some of the signals that converge on these neurons are transmitted by rather generic inhibitory [e.g. gamma-aminobutyric acid (GABA)] and stimulatory (e.g. glutamate) neuroamines. But two neuropeptides have special roles in the control of GnRH secretion: kisspeptin and neurokinin B.[30–33]

Kisspeptin refers to a family of closely related peptides coded by the *KISS1* gene. Inactivating mutations in the *KISS1* gene or the gene for the kisspeptin receptor, *GPR54*, are associated with idiopathic hypogonadotrophic hypogonadism (IHH, abnormally low gonadotropin and gonadal steroid levels) and failure to undergo spontaneous puberty in both humans and animal models.[34] In animal models, including both rodents and primates, *KISS1* transcriptional activity increases significantly just before puberty, and *GPR54* expression has been localized on GnRH-secreting neurons.[35,36] Some *KISS1* variants with longer blood half-lives have also been associated with precocious puberty in humans.[34] *KISS1* and *GPR54* knockout models have also demonstrated that kisspeptin signaling is necessary for the normal pubertal activation of pulsatile GnRH secretion in animal models while centrally administered kisspeptin acutely stimulates pulsatile GnRH secretion.[37] Kisspeptins, however, may serve not as independent triggers for puberty but rather as necessary amplifiers of upstream regulatory mechanisms.[165] Their expression appears to be suppressed prior to puberty by transcriptional repressors.[166]

It has been proposed that neurokinin B (NKB), a distinct peptide that is co-secreted by some kisspeptin-secreting neurons, also provides a necessary signal for normal puberty. Mutations in the gene coding for the peptide (*TAC3*) and its receptor (*TAC3R*) have been associated with IHH in humans, and NKB neuronal projections have been traced to GnRH neurons in ultrastructure studies.[32] Together with other tachykinins and dynorphin, NKB is expressed in some kisspeptin-secreting neurons, known as KNDy neurons, and serves to regulate them.[170]

Kisspeptin and NKB neurons in the arcuate nucleus of the hypothalamus express estrogen receptors. Their activity appears to be subject to steroid feedback, though prepubertal restraint of kisspeptin neurons seems to be steroid-dependent in rodents but not in primates.[165] Kisspeptin neurons are sexually dimorphic in their abundance in the hypothalami of rodent models, and it has been proposed that the organizing effects that steroids have on the brain early in development may involve organizing effects on kisspeptin and NKB neurons.[33]

Neuropeptide Y (NPY) is another neuropeptide that may help to regulate GnRH secretion. Its effects are primarily inhibitory. Central administration of NPY inhibits pulsatile GnRH secretion in gonadectomized rhesus monkeys.[38,39] But it is unclear whether NPY acts directly on GnRH neurons or through the mediation of other signaling pathways.

Finally, mention must be made here of leptin, a peptide produced by adipose tissue, which may play an important role in the regulation of the HPG axis. While it was proposed early on that leptin might exert direct control of GnRH secretion,[40–42] that now appears unlikely, since GnRH neurons do not express leptin receptor.[43] More will be said about leptin and its putative role in pubertal timing in the next section.

The systems biology of GnRH secretory control is an area of intense research effort at present and much remains to be elucidated. It appears, however, that a number of signaling pathways converge on GnRH neurons with widespread inputs within and beyond the hypothalamus. Rather than positing a single, upstream "trigger" for puberty, the hypothesis gaining the most traction is that GnRH neurons integrate the various inhibitory and stimulatory signals in ways that ultimately affect pulsatile GnRH secretion. In the next section, some of the broader genetic, epigenetic and environmental influences that are thought to affect pubertal timing will be considered.

Upstream factors influencing pubertal timing

There are many upstream factors that influence pubertal timing, as discussed below.

Genetic factors

The biological factors that influence pubertal timing can be broadly classified as genetic, epigenetic, and environmental, although these domains always interact. Genetic influences on puberty are apparent in a number of clinical pathologies.[44] But evidence for genetic factors influencing normal, non-pathological variation in pubertal timing comes primarily from studies of concordance between different degrees of relatives. Studies comparing monozygotic twins with dizygotic twins and non-twin siblings, for example, indicate that the heritability of menarcheal age in girls is comparable to the heritability of adult height.[45–47] Studies of this kind usually underestimate the potential range of environmental variability, however, and so only provide a relative sense of underlying genetic determination, not a precise measurement. Like height, pubertal timing is likely to be subject to the influence of many genes of individually small effect, an assumption that is consistent with the nearly normal distribution of menarcheal age and other indices of pubertal timing in most populations.[48]

Epigenetic factors

Accumulating evidence suggests that excitatory and inhibitory inputs to GnRH pulse-generating neurons are under epigenetic regulation. This means that developmentally- and ecologically-mediated changes in the expression of genes such as *KISS1* and *TAC3* lead to the onset of puberty, rather than puberty being initiated by the maturation of GnRH neurons themselves.[170] For example, in female rodents, a transcriptional silencer complex in the Polycomb group appears to silence *Kiss1* genes until the onset of puberty.[166] Parallel results have been found in males. Research in primates and rodents indicates that a category of common transcriptional repressor, zinc finger (ZNF) motifs, maintains the juvenile state of GnRH neurons by repressing the gene network that causes their pulsatile

action. Researchers examined the hypothalamus of agonadal male rhesus monkeys at the moment when GnRH neurons had begun pulsatile secretion. They found that several ZNFs showed decreased expression at the same time that *KISS1* and *TAC3* expression increased.[167]

Environmental factors

Environmental influences on pubertal timing are apparent in well-documented patterns of socioeconomic variation within populations and in the changes in pubertal timing that often accompany migration or other movement between ecological and socioeconomic conditions.[48,49] Particular attention has been paid to two types of environmental factor associated with variation in pubertal timing: energetics and psychosocial stress. In addition to correlative evidence, both of these factors are associated with important neuroendocrine pathways regulating GnRH secretion.

Energetics

Frisch and colleagues first called explicit attention to the relationship between energetics and puberty in the 1970s, hypothesizing that a certain level of stored fat was necessary to trigger menarche in girls.[50–52] While this specific hypothesis has been subject to intense criticism,[53–57] the relationship between good nutrition, and hence rapid growth, in childhood and early puberty is more generally accepted. Experimental evidence from animal models including rodents and sheep shows that variation in energy intake and energy expenditure in the prepubertal period can change the timing of puberty.[58–60] Although similar experiments cannot be carried out in humans, both height for age and weight for height in late childhood are significant predictors of pubertal timing, and childhood athletic training and childhood malnutrition are associated with pubertal delay.[61–64]

It is important to keep in mind three distinct metrics when considering the relationship of growth to pubertal timing: rate of growth (usually height velocity), final height and age at puberty. Rate of growth and timing of puberty co-vary; that is, faster growth in childhood is associated with earlier age at puberty. The relationship between rate of growth and final height across populations is more variable, dependent on the genetic potential for adult height within each population.

Pathologies that are associated with short stature are almost invariably also associated with late or absent puberty (Table 5.1). There is a generally inverse relationship between adult height and pubertal timing at the population level as well, despite considerable variability. In contrast, the secular trend toward earlier puberty that has been well documented in many developed and developing countries over the past century has generally also been a secular trend toward greater adult height.[48,49,66] The coincidence of pathologies of growth

Table 5.1: Pathological causes of slow or stunted growth that are also associated with pubertal delay or absence.[65]

Anorexia
Cardiovascular disease (cyanotic heart disease and congestive heart failure)
Chronic anemias
Chronic infection
Constitutional delay of growth
Cushing syndrome
Diabetes mellitus (especially Mauriac syndrome)
GH deficiency
GH insensitivity
IGF-1 deficiency
Hypothyroidism
Intrauterine growth retardation
Malnutrition
Malabsorption
Prader–Willi syndrome
Pulmonary disease
Psychosocial dwarfism
Renal disease
Turner's syndrome

and pathologies of pubertal maturation suggests that many common physiological mechanisms underlie both processes. The covariance of adult height and pubertal timing across time suggests that many environmental factors also influence both processes.

Several pathways connect information about energy balance with the neuroendocrine mechanisms controlling GnRH secretion. Among the important peripheral signals of energy balance are insulin and leptin. Insulin is secreted by the pancreas to promote glucose uptake from the circulation. Daily rates of insulin production are positively correlated with energy balance.[67–69] Upstream of HPG axis function, insulin receptor (IR) is expressed in the mouse hypothalamus and in immortalized GnRH cell lines.[70,71] Suppression of IR in the mouse hypothalamus results in a reduction in GnRH pulsatility.[70] There is thus a potential for insulin to directly regulate pulsatile GnRH release, although the effectiveness of peripheral insulin in exerting this control has not been demonstrated. Downstream, adipose cells are important targets of insulin action, and estrogens facilitate the action of insulin on adipose tissue in women, promoting fat storage.[72,73]

Leptin is a peptide secreted by adipose cells. Levels of leptin secretion vary with fat mass, but they also vary as a consequence of estrogen and insulin stimulation.[74–82] Therefore, females secrete higher levels of leptin per fat mass than males, and individuals of both sexes in positive energy balance secrete more leptin per fat mass than individuals in negative energy balance.

Leptin receptor (LepR) is not expressed by GnRH-secreting neurons,[43] but it is expressed by other hypothalamic cell populations, including kisspeptin-secreting neurons.[31,34] Thus, there is a potential for leptin to indirectly contribute to the regulation of pulsatile GnRH secretion. There is good evidence that this control can be exerted in adult women. For example, in patients with amenorrhea associated with low energy balance, exogenous elevation of peripheral leptin levels results in increases in LH pulse frequency, the number of secondary maturing follicles and circulating estradiol levels.[83,84]

The relationship of insulin and leptin to pubertal timing is more complex. The pubertal period is a period of transient insulin resistance, meaning that circulating insulin levels rise.[85,86] This increase in insulin resistance is caused by increased circulating levels of insulin-like growth factor-1 (IGF-1) during the pubertal growth spurt. IGF-1 reduces the sensitivity of peripheral adipose tissue to insulin, therefore resulting in an increase in baseline insulin necessary to regulate blood glucose levels.[87,88] The increase in peripheral insulin may be correlated with an increase in insulin signaling in the hypothalamus, but this has not been demonstrated. It would seem unlikely that this rise in insulin could contribute to pubertal initiation, however, since it appears to be a consequence of puberty, not an antecedent. Other evidence suggests that prepubertal insulin levels may influence pubertal timing. Women who develop type 2 (adult-onset) diabetes have earlier menarcheal ages than controls, as do first order relatives of type 2 diabetics.[89] In contrast, women with type 1 diabetes have historically entered puberty later than controls, and modest delays in some measures of pubertal development continue even with highly controlled insulin treatment.[168]

Exogenous administration of leptin to prepubertal mice accelerates vaginal opening, an external sign of reproductive maturation.[90] In primates, including humans, however, increases in circulating leptin, like those of insulin, occur as a consequence of puberty, not as an antecedent.[91,92] Some researchers have suggested that leptin is a permissive gate for puberty in humans, meaning that adequate leptin levels are necessary, although not in themselves sufficient, for puberty to occur.[93] Even this hypothesis is in doubt, however, since there are documented cases of individuals with pathological failure of adipose tissue development and extremely low leptin levels who have nevertheless experienced normal puberty and even given birth.[94]

Rather than being a trigger or a gate for puberty, leptin and insulin levels probably contribute to hypothalamic signaling pathways that accelerate or retard pubertal timing without completely determining it. Since both hormones are also important signals of energy balance, a modulating role would be consistent with the documented modulating influence of energy balance on pubertal timing. There is evidence that both insulin and leptin act on kisspeptin neurons in the hypothalamus, which would provide at least one pathway for such a modulatory effect.

Psychosocial stress

In addition to energetics, there is considerable evidence suggesting that psychosocial stress can influence the timing of puberty, although the evidence can be conflicting. Early studies by Boas documented late maturation among children institutionalized in orphanages.[95] More recent studies find evidence that institutionalization under conditions of chronic maltreatment early in life or a history of childhood abuse can lead to early puberty.[96–98]

Psychosocial stress has also been associated with early puberty in a different context. A number of studies (but not all) have found that girls raised in "father absent" households have earlier ages at menarche than their otherwise similar peers.[99–103] The size of the effect is relatively small, especially when controlled for genetics, and the effect appears limited to Western, educated, industrialized, wealthy, democratic populations.[169] But several researchers have noted that an acceleration of maturation is predicted to occur when adult mortality risk is high by the branch of evolutionary theory known as life history theory.[102,104–106] It has been suggested that the environment of upbringing might provide important signals about the quality of the environment to be expected in adulthood, and that humans may have evolved to adjust the tempo of maturation in accordance with these signals.

Psychosocial stress is known to affect the HPG axis in animal models.[107–110] Proving that the human HPG axis is sensitive to psychosocial stress independent of other factors is more difficult.[111,112] Most research focuses on interactions between the hypothalamic–pituitary–adrenal (HPA) axis, which is activated under conditions of psychosocial stress, and the HPG axis.[111,113,114] Activation of the HPA axis can be shown to suppress HPG axis function, especially if HPA activation is chronic. High levels of cortisol (the steroid produced by the adrenal gland in response to HPA activation) have also been associated with early pregnancy loss in some studies.[115,116] However, psychosocial stress is only one cause of HPA axis activation. Other physical and metabolic stresses, including energetic stress, can elevate HPA activity.[117,118] Thus, it is not possible to infer from evidence of HPA activation that psychosocial stress is the cause of that activation in any particular situation.

Importantly, the "father absence" hypothesis on the one hand and research on cortisol's impact on HPG axis function on the other generate opposing predictions about the direction of the influence of the HPA axis on the timing of puberty. These findings could be reconciled if chronic psychosocial stress were found to result in diminished activation of the HPA axis, or if psychosocial stress were to act through mechanisms other than the HPA axis.

In summary, a broad range of environmental factors can be shown to influence puberty and reproductive function more generally. Energy balance and psychosocial stress have

both attracted attention in humans. Other factors, such as day length and temperature, figure prominently in other mammals.[119] The relatively small population of GnRH neurons in the hypothalamus provides a final common pathway for the integration of information regarding these factors in modulating the timing of puberty.

Downstream consequences of pubertal activation of the hypothalamic–pituitary–gonadal axis

Reactivation of pulsatile GnRH secretion is the central event of puberty. In humans, however, it is an unobservable event. What can be observed are its downstream consequences. These consequences begin with downstream parts of the HPG axis, but soon ramify to include a host of somatic and central nervous system tissues and physiological processes. If the GnRH neurons are the final common pathway for central inputs to the HPG axis affecting puberty, gonadal steroid production can be considered the final common pathway for outputs from the HPG axis to the rest of the body. The extremely broad reach of gonadal steroids in transforming the rest of the body at puberty reflects the fact that puberty is, as noted in the introduction to this chapter, a major life history transition, almost akin to metamorphosis, from an organism whose most basic concerns are staying alive and growing to one concerned with staying alive and reproducing.

Because the downstream consequences of pubertal maturation are so numerous, it will not be possible to review them all here. Some are discussed at greater length in other chapters in this volume. This text will be confined to briefly touching on the downstream consequences for the HPG axis itself, for the pubertal growth spurt and for the development of the most prominent secondary sexual characteristics. These are the downstream consequences that are most often observed in making inferences about puberty, and some of the dangers and assumptions in making those inferences will occasionally be noted.

Downstream effects on the hypothalamic–pituitary–gonadal axis

The earliest observable change in HPG axis activity associated with puberty is the appearance of sleep-related pulses of LH that subside during the daytime.[120,121] These are assumed to reflect sleep-related pulsatile release of GnRH, and the circadian pattern suggests some influence of central circadian pacemakers. Over a variable period of time, usually in the order of weeks to months, pulsatile LH secretion extends to the daytime and pulses increase in magnitude. FSH pulses, which occur at much lower levels, may also become observable at this time. The appearance of sleep-related LH pulses occurs earlier in girls than in boys, as is true of virtually all pubertal indicators.

Gonadal steroid production increases as gonadotropin release patterns become more robust. In girls, rising estradiol levels are assumed to reflect the initial recruitment of primary follicles, the production of testosterone by the outer layer of theca cells in those follicles under the influence of LH, and the aromatization of some of the testosterone into estradiol by the inner granulosa cells of those follicles under the influence of FSH.[122] Circulating levels of gonadal steroids do not reach high levels at first, and there is no evidence of ovulation or menstrual bleeding. Production of testosterone often exceeds the rate of aromatization to estradiol at this stage. In boys, rising testosterone levels are assumed to reflect increasing activity of Leydig cells outside the seminiferous tubules. Proliferation of Sertoli cells inside the tubules occurs as a consequence, although there is no evidence of sperm in urine at this stage.[123,124]

In girls, rising levels of estradiol production from the ovaries cause proliferation of the endometrial lining of the uterus. In the absence of progesterone support, the endometrial lining will eventually slough off.[125,126] The first occurrence of menstrual blood, known as menarche, is often taken as a milestone in female pubertal maturation, but it does not really represent a significant functional boundary in the development of female reproductive potential. Menarche does not, for instance, indicate ovulation and the production of viable gametes. Nor by itself does it signify the ability to successfully initiate gestation. It is, however, a notable external event, often imbued with cultural significance. A similar external marker in boys does not exist. Beard growth and voice change are highly variable in manifestation. Immature sperm may appear in urine at an early stage, but this is rarely observed. Ejaculation and nocturnal emission are extremely variable between individuals and may not occur at early stages of pubertal maturation at all.[127,128]

Ovulation usually first occurs some time after menarche in girls.[129] Ovulation and menstruation become increasingly regular over a period of years. Testosterone to estradiol ratios may remain higher during this period than among fully mature women, and luteal progesterone levels are lower on average.[122,130,131] Peak fecundity, as reflected by the frequency of ovulation and levels of gonadal steroid secretion, usually is not achieved until nearly a decade after menarche. In boys, sperm production, sperm quality and ejaculatory volume reach mature levels more quickly, usually within 5 years of the first signs of pubertal development.[132]

The pubertal growth spurt

Although other hormones, including insulin, growth hormone and IGF-1, play a role in promoting growth at puberty and before, the pubertal growth spurt itself — the relatively rapid acceleration and deceleration of linear growth that normally brings growth in stature to an end — is now understood to be primarily a consequence of the action of estradiol in both sexes.[133,134] In females, the primary source of estradiol is the ovary. In males,

testosterone is secondarily converted to estradiol by aromatase in cartilage and bone of the growth plates. Individuals who are chromosomally male but with complete androgen insensitivity syndrome due to disabling mutations of the androgen receptor gene nevertheless experience a normal growth spurt.[134] Although testosterone and other androgens cannot have any direct effect in these individuals, locally converted estradiol still stimulates a normal pubertal growth spurt. In contrast, males who lack functional estradiol receptors or functional aromatase enzyme do not experience a growth spurt – either the acceleration phase or the deceleration. Instead, there are documented cases of such individuals continuing to grow at a prepubertal pace into their thirties[134–137] (Fig. 5.1). In contrast, individuals with complete androgen insensitivity due to a defect in the androgen receptor gene undergo normal pubertal growth spurts, reflecting the fact that aromatase conversion of androgens to estrogens is still intact[138,139] (Fig. 5.2).

Estradiol receptor is expressed both by active chondrocytes and by osteoblasts and osteoclasts in the growth plates of growing bones.[134] The pubertal acceleration of growth involves the action of estradiol in stimulating chondrocyte proliferation and growth, while the rapid deceleration and eventual closure of the growth plates is due to the actions of estradiol in stimulating mineralization by osteoblasts and opposing demineralization by osteoclasts. Both of the major estradiol receptor subtypes are probably involved, so that chondrocyte stimulation predominates at lower estradiol concentrations and osteocyte stimulation predominates at high estradiol concentrations.

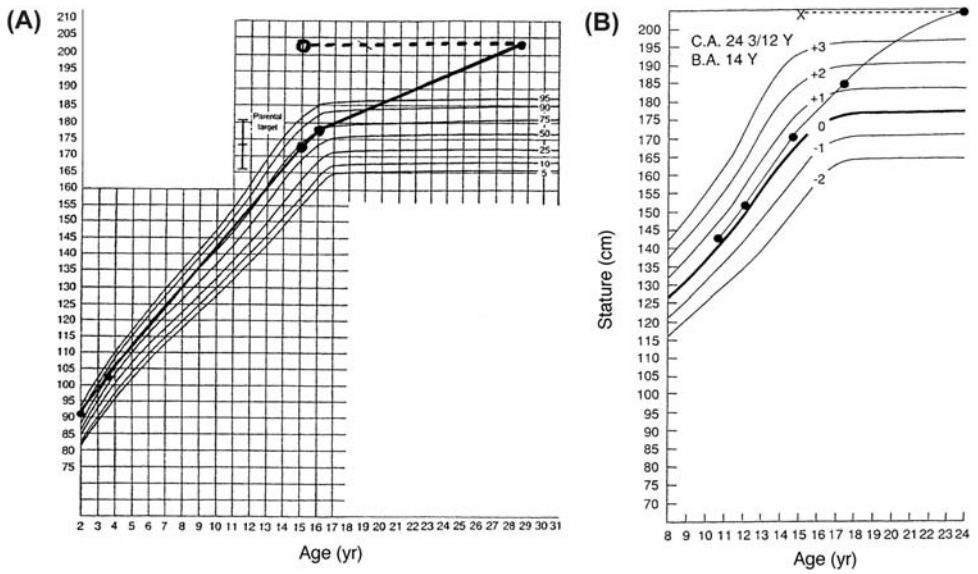

Fig. 5.1

(A) Growth chart from a man with a disruptive mutation of the estrogen receptor alpha gene[134]; (B) growth chart of a man with a disruptive mutation in the aromatase gene, *CYP19*.[135] *From Juul A. The effects of oestrogens on linear bone growth.* Hum Reprod Update. *2001;7:303–313.*

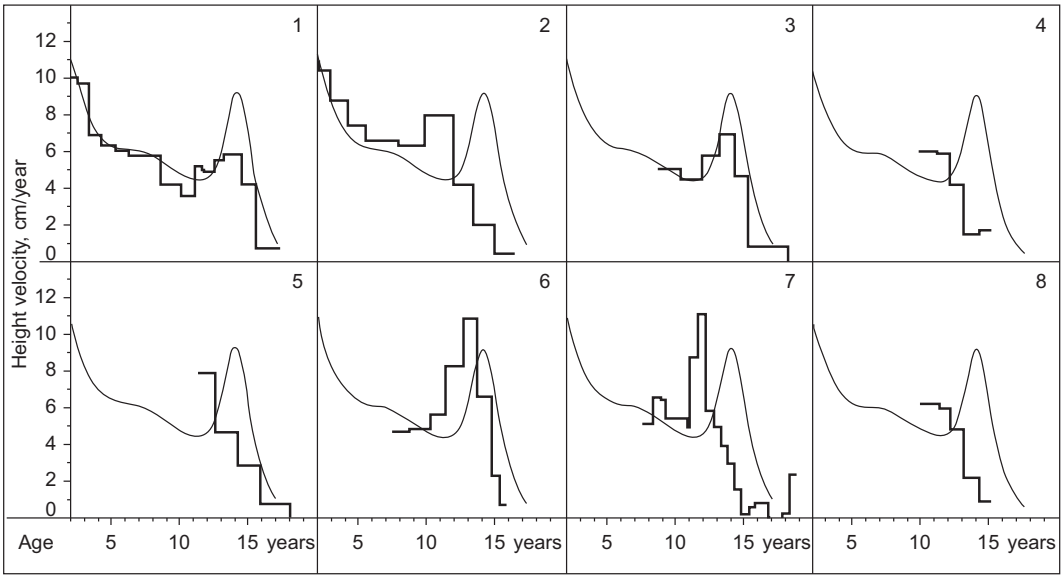

Fig. 5.2

Growth velocity charts for eight patients with complete androgen insensitivity compared with curves for normal boys. *From Zachmann M, Prader A, Sobel EH, et al. Pubertal growth in patients with androgen insensitivity: indirect evidence for the importance of estrogens in pubertal growth of girls.* J Pediatr. *1986;108:694–697.*

Secondary sexual characteristics

All the major sexually dimorphic characteristics of adult males and females are consequences of the action of gonadal steroids circulating at adult levels. The sequence of appearance of major secondary sexual characteristics tends to follow the sequence of elevation of steroid levels.[140] Pubic and axillary hair is stimulated by androgens in both sexes and thus tends to appear early in the pubertal sequence in girls.[141] These androgens are produced by the adrenal gland. When adrenal androgen production is pathologically elevated, as in cases of untreated congenital adrenal hyperplasia, precocial growth spurts can result.[142,143] Female breast development and pelvic remodeling are stimulated by estradiol and thus tend to occur later.[144,145] Pelvic remodeling, important for parturition, occurs internally and at a rapid rate and is thus difficult to measure; its degree is underestimated by measurements of biiliac breadth.[145] Menstruation in girls occurs only when estradiol levels have reached a high enough level for long enough to stimulate sufficient endometrial growth, and thus menarche tends to occur after the initiation of breast development and usually during the decelerating phase of pubertal growth.[146] Testis growth in boys is a consequence of seminiferous tubule development and the proliferation of Sertoli cells, and thus occurs early in the pubertal sequence in boys. The growth spurt

itself, both in height and in shoulder breadth and arm length, occurs later, when higher levels of circulating testosterone result in higher levels of local conversion to estradiol. Penis growth is a result of a different secondary local conversion of testosterone to dihydrotestosterone, and occurs more or less in synchrony with the growth spurt.[146]

Changes in body composition are also important downstream consequences of gonadal steroid production.[147,148] Estradiol stimulates adipose tissue growth in girls, particularly in the breasts and gluteofemoral region, acting in synergy with insulin.[148,149] Testosterone, on the other hand, acting through androgen receptors, inhibits adipose tissue growth and stimulates muscle anabolism in boys.[150,151] It is important to realize that these changes in body composition are consequences of pubertal maturation, not antecedents.[91,152] Increases in fat percentage in girls are correlated with pubertal stage, but they are not the primary causes of pubertal maturation.

As with the height spurt, precocial development of secondary sexual characteristics can occur as a result of pathological or idiosyncratic overproduction of adrenal steroids.[143] The adrenal gland normally produces weak androgen hormones whose significance is still debated.[142] These androgens can be locally converted to estrogens in various tissues, including adipose tissue.[153] In postmenopausal women this conversion of adrenal androgens to estrogens (so-called "extragonadal estrogen production") is the principal source of circulating estrogens, levels of which are directly correlated with adiposity.[154,155] Increasing rates of childhood obesity and overweight are thought to be largely responsible for a trend toward early breast development in girls in some populations.[156,157] It is important to realize, however, that extragonadal estrogen production is not a consequence of HPG axis activation and thus does not represent puberty. Nor can it result in ovulation or normal fecundity.

Summary

As complicated as it is, human puberty can be thought of according to a relatively simple model, expressed in Fig. 5.3. This model can be thought of as an "hourglass", with a number of factors and pathways converging on pulsatile GnRH secretion as the "on/off switch" of the HPG axis, and a ramifying set of downstream consequences of gonadal steroid production as the final product of the HPG axis.

At the heart of the pubertal process is the reactivation of pulsatile GnRH secretion by the relatively small population of hypothalamic GnRH neurons. The capacity for this secretion is fully developed years in advance of puberty, and pulsatile secretion probably occurs in both the fetus and the neonate. In gonadectomized rhesus monkeys, reactivation of the HPG axis occurs spontaneously at a relatively normal age. No simple physiological signals responsible for the reactivation of GnRH pulsatility has yet been discovered.

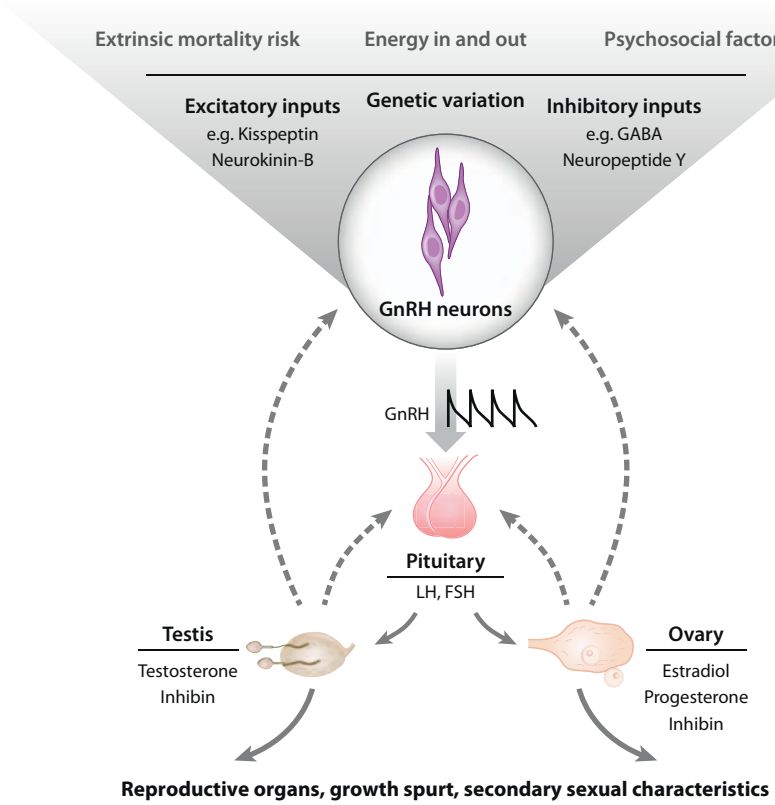

Fig. 5.3

A schematic model of human puberty, including upstream modulators and downstream consequences. Upstream modulating pathways converge on the reactivation of pulsatile GnRH secretion. Downstream consequences emanate from changes in circulating levels of gonadal steroids.

Instead, the spontaneous activation of GnRH neurons appears to result from an increase in excitatory signals and a decrease in inhibitory signals. Activity of the GnRH neurons is subject to control and modulation by a number of upstream neuron populations secreting a variety of neurotransmitters and neuromodulators. Among those with inhibitory effects on GnRH secretion are GABA and NPY. Among those with stimulatory effects are kisspeptin and glutamate. Other pathways further upstream, such as those involving insulin, leptin and the HPA axis, integrate information about important aspects of the environment and the state of the organism, such as photoperiod (not addressed in this chapter but well documented in many non-human mammals such as rodents), energy balance and psychosocial factors.

At the other end of the HPG axis, production of gonadal steroid hormones results in the maturation of the gonads as producers of mature gametes as well as the mature function of other parts of the reproductive system, such as the endometrium and breasts in girls and accessory glands in males. The pubertal growth spurt is also a downstream consequence of gonadal steroid production along with the development of secondary sexual characteristics and changes in body composition. The aspects of puberty that are normally downstream consequences of gonadal maturation can also occur as consequences of excessive adrenal androgen production or excessive conversion of adrenal androgens to estrogens. Secondary sexual characteristic development that is not driven by the HPG axis, however, cannot result in its activation and in adult fertility, and thus should not be confused with true puberty.

The search for "triggers" of human puberty has so far been unsuccessful. It may be more useful to think of normal puberty as a process of innate maturation, the timing of which can be modulated by factors such as nutrition and stress.

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Internet resources

Hot Topic: Endocrinology resources on the Internet. *J Clin Endocrinol Metabol*. http://jcem.endojournals.org/content/86/7/2942.full.

A journal article, freely available, on how to access Internet resources related to endocrinology

You and your hormones. http://www.yourhormones.info/.

A layperson's guide, produced by the Society for Endocrinology.

The major professional society websites all have links to relevant resources and post recent news items and information:

Society for Endocrinology. http://www.endocrinology.org/index.aspx.

Society for Behavioral Neuroendocrinology. http://www.yourhormones.info/.

American Neuroendocrine Society. http://www.neuroendocrine.org/.

Endocrine Society. http://www.endo-society.org/.

Some children's hospitals also provide resources or links on their websites, although these are more often relevant to topics such as diabetes than to puberty per se. One example is:

University of Maryland Children's Hospital. *Pediatric Endocrinology Resources*. http://www.umm.edu/pediatrics/pediatric_endocrinology_resources.htm.

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CHAPTER 6

Endocrine control of growth

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Overview of the endocrine system, hypothalamic-pituitary-gland axes, hormones relevant to growth

The hypothalamus, located on the undersurface of the brain, integrates signals from the brain and circulation to control production and release of hormones by the anterior pituitary gland. The hypothalamus releases hormones into the portal vessels for rapid transport to the anterior pituitary gland. Growth hormone (GH) releasing hormone (GHRH), thyrotropin releasing hormone (TRH) and gonadotropin releasing hormone (GnRH), released by the hypothalamus, stimulate release of GH, thyroid stimulating hormone (TSH) and the gonadotropins luteinizing hormone (LH) and follicle stimulating hormone (FSH), respectively. The production of each of these hormones is regulated through feedback by hormones produced by the peripheral target tissues forming a feedback loop. GHRH production by the hypothalamus if regulated by GH-dependent levels of insulin-like growth factor 1 (IGF-1). TRH production is regulated by TSH-dependent levels of triiodothyronine (T3). GnRH production is regulated by gonadotropin-dependent levels of the gonadal hormones inhibin and estradiol (in both males and females). Somatostatin, released by the hypothalamus, inhibits the release of GH. GH, IGF-1, thyroid hormone and sex hormones are all involved in the regulation of linear growth at different ages.

Growth hormone (GH) and insulin-like growth factor 1 (IGF-1)

The primary hormone involved in linear growth is GH secreted by the pituitary gland. It is regulated by the GHRH produced by the hypothalamus (Fig. 6.1).

GH is secreted in pulses throughout the day with the majority of the pulses occurring at night. During sleep, GH production increases during the Rapid-Eye-Movement (REM) sleep phase. GH secretion also occurs throughout the day and is suppressed by food. GH is found in the circulation bound to GH binding protein (GHBP), which is derived from

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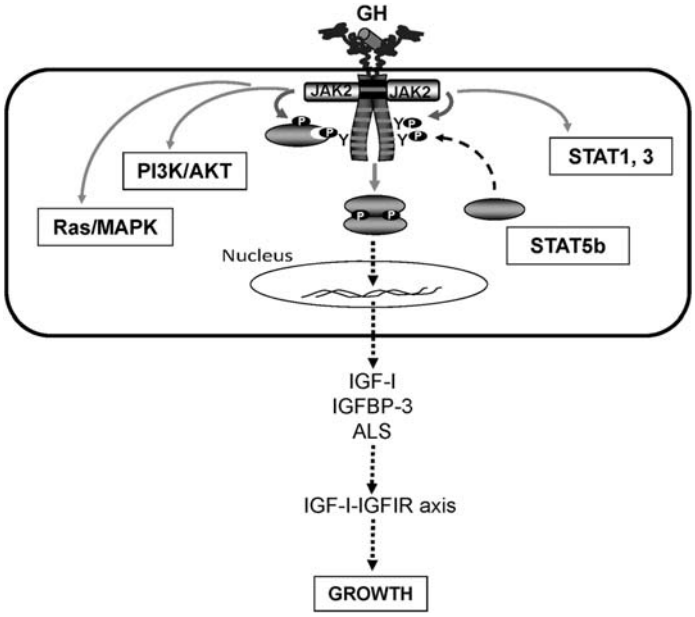


Fig. 6.1

Growth hormone – insulin-like growth factor 1 cascade.

ALS, acid labile subunit; *GH*, growth hormone; *GHBP*, growth hormone binding protein; *GH-R*, growth hormone receptor; *IGF*, insulin-like growth factor; *IGFBP*, insulin-like growth factor binding protein; *IGF-R*, insulin-like growth factor receptor; *kDa*, kilodalton.

the extracellular domain of the GH receptor. GH binds the GH receptor on the target tissue to stimulate intracellular signaling of the GH receptor through the Jak-Stat pathway promoting the production of insulin like growth factor I (IGF-1) and insulin like growth factor binding protein 3 (IGFBP-3). IGF-1 is primarily produced in the liver but can be produced by other tissues. IGF-1 is secreted into the circulation and carried by IGFBP-3, as a binary complex, and the acid labile subunit (ALS) as a ternary complex to the target tissue for its action. IGF-1 is also produced at the local level. The activity of IGF-1 at the local level, including its availability to stimulate the cell surface IGF-1 receptor, is regulated by binding to six different IGF binding proteins (Fig. 6.2).

At the growth plate, GH acts on the resting cells of the growth plate to promote their proliferation and entry into the active portion of the growth plate denoted as the proliferative zone. IGF-1 acts at the proliferative zone to promote cartilage proliferation and differentiation into hypertrophic chondrocytes. The action of hypertrophy of the chondrocytes promotes the linear growth of the bone at the growth plate by enlarging the growth plate. The hypertrophic chondrocytes differentiate and ultimately are calcified leading to maturation of the growth plate.

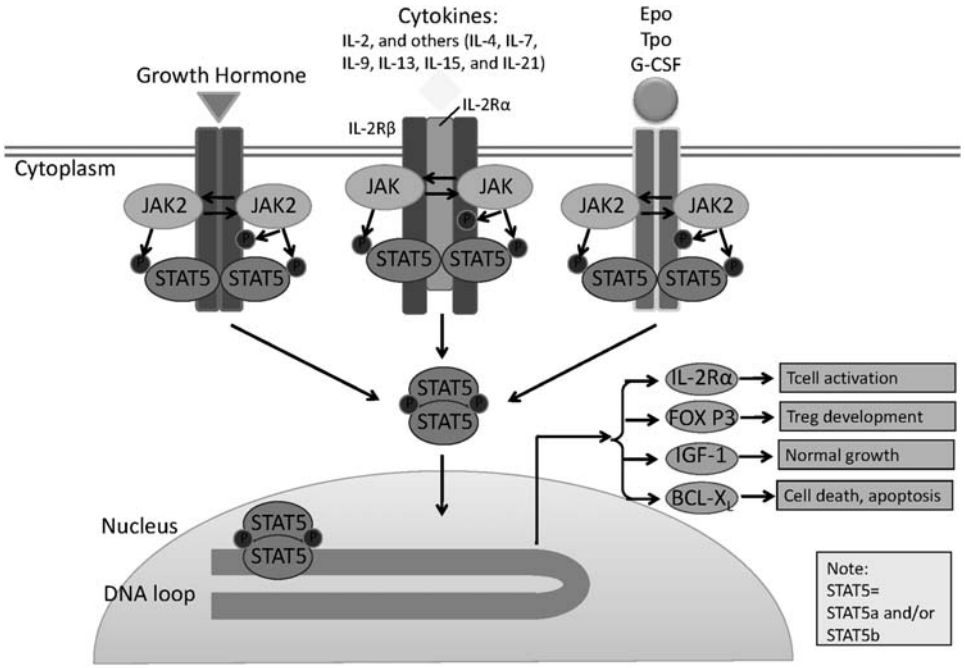


Fig. 6.2

Growth hormone-insulin-like growth factor cascade at the cellular level.
ALS, acid labile subunit; *GH*, growth hormone; *GHBP*, growth hormone binding protein; *GH-R*, growth hormone receptor; *IGF*, insulin-like growth factor; *IGFBP*, insulin-like growth factor binding protein; *IGF-R*, insulin-like growth factor receptor; *IGFBP-3R*, insulin-like growth factor binding protein 3 receptor; *IGF2-R/M6PR*; insulin-like growth factor 2 receptor/mannose 6-phosphate receptor; *kDa*, kilodalton.

The endocrine function of the GH-IGF-1 pathway is active throughout the life of the organism.[1–4] However, during fetal life, GH activity is quite low. During fetal life, growth is promoted by placental hormones as well as local production of IGF-1 and IGF-2. Children with pituitary GH deficiency have relatively normal linear growth *in utero*. In the early postnatal period, GH production by the pituitary gland and IGF-1 and IGFBP-3 production by the liver and other tissues increases and the endocrine action of the GH-IGF-1 axis increases over time. In the first year of life, growth is less dependent upon the GH-IGF-1 axis than it is on thyroid hormone and nutritional regulation. However, late in the first year of life, the GH-IGF-1 axis become the major regulators of endocrine-related growth. GH and IGF-1 are the major endocrine regulators of growth between the first year of life and the entry into puberty. During the pubertal growth spurt, GH production is increased by or in response to increased levels of testosterone and estrogen. As the growth plates close as the pubertal growth spurt comes to an end the GH-IGF-1 axis becomes less active with reduced levels of GH and IGF-1 produced in young adult life. The GH-IGF-1

axis remains active throughout adult life at lower levels. The endocrine action of GH and IGF-1 during adult life is primarily related to the maintenance of muscle and bone health and body composition. In addition to the linear growth component of GH action, GH has important actions on regulating metabolism primarily at the level of the fat tissue. GH is a metabolic hormone that causes release of fatty acids from the fat tissue for fuel during times of fasting. This is one reason why GH levels are suppressed following a meal to allow for storage of fat for future use.

Synthesis of GH by the pituitary gland is largely regulated by GHRH acting on pituitary somatotropes. GHRH binds to its GHRH receptor on the surface of pituitary somatotropes. The GHRH receptor is a member of the seven transmembrane loop G protein coupled receptor class. Stimulation of the GHRH receptor by GHRH activates an increase in cyclic adenosine monophosphate (cAMP) production in the pituitary cells. The increase in cAMP activates Protein Kinase A which phosphorylates a cytoplasmic transcription factor, CREB (cAMP response element binding protein). Phosphorylated CREB translocates into the nucleus where it binds to specific transcription response elements in the promoter region of the GH gene and activates transcription of the *gh* gene. The *gh* gene is located on chromosome 17. Transcription of the *gh* gene is also regulated by other factors including positive regulation by thyroxine and negative regulation by cortisol. Transcription and translation of the full-length GH gene leads to synthesis of the 22 kDa form of GH by the pituitary gland. Alternative splicing of the GH gene leads to synthesis of a 20 kDa form. The 20 kDa form of GH makes up approximately 10% of the circulating GH. GHRH also stimulates release of previously formed GH. Somatostatin negatively regulates GH production and release. The normal pulsatile secretion of GH is a balance between GHRH and somatostatin levels. GH secretagogues act at the GH secretagogue receptor synergistically with GHRH to promote GH release. Ghrelin, a hormone produced by the stomach, also regulates GH secretion through the GH secretagogue receptor. Other endogenous agents that may impact GH secretion include opioids, calcitonin and glucagon. Similar to other endocrine feedback loops, GH feeds back to inhibit its own synthesis and release at the level the hypothalamus. This is likely through a combination of increased somatostatin and reduced GHRH production. In addition, IGF-1 generated in response to GH feeds back to inhibit GH synthesis and release by the pituitary gland. The pulsatile nature of GH secretion and action at target tissues may be important. This may impact the response of target tissues to GH's metabolic action and IGF-1 production.

The GH receptor is a member of the cytokine receptor family. This group of receptors is involved in regulation of multiple processes including growth of hematopoietic and immunoregulatory cells and immune function. When GH binds to the GH receptor it interacts with two receptor molecules to promote dimerization. Dimerization of the two receptor molecules leads to activation of the intracellular signaling pathway by activating Jak kinase.

Fetal, infancy, childhood, and adolescent endocrine controlled growth characteristics

Studies in domestic animals demonstrate that pulsatile secretion of GH and other pituitary hormones is demonstrable in fetal life. A gradual increase in circulating GH occurs during the first 12 weeks of pregnancy reaching the peak at 20–24 weeks and declining toward birth. Early changes in serum GH concentrations appear to parallel the known development of the hypothalamic secretion of GHRH and somatostatin. At term, GH levels are 20–30 times higher than those observed in childhood but are continuously elevated and lack the pulsatile pattern observed in childhood and adult life. However, these elevated levels of GH are not associated with elevated levels of IGF-1 in the fetus. Therefore, there is relative resistance to the effects of GH in the fetus. Thus, GH is not the predominant determinant of fetal growth. This is demonstrated by the observation that infants with mutations in the GH gene, or GH insensitivity due to mutations of the GH receptor, have normal size at birth when adjusted for maternal size.

In addition to rarely identified genetic mutations in humans that have helped explain the role of the GH-IGF-1 axis during fetal and postnatal growth, a number of illustrative knockout models in mice have helped understand the role of different components of the GH-IGF-1 axis. The importance of the GH-IGF-1 axis is clear from the fetal demise seen in some of the knockout models. In addition, the role of IGF-1 and IGF-2 on fetal growth is shown to be critical. Children with mutations in the IGF-1 gene, abnormalities of the IGF-1 gene and abnormalities of the IGF receptor gene all have *in utero* growth retardation. Surprisingly, loss of the insulin gene does not appear to alter body size. However, mutations of the insulin receptor gene can lead to *in utero* growth retardation. This suggests that the IGF-1 receptor and insulin receptor both have important roles in fetal growth. This is not surprising since fetal isoforms of the insulin receptor have higher binding affinity for IGF-1 and IGF-2 than isoforms expressed postnatally. Hyperinsulinemia associated with maternal hyperglycemia and maternal diabetes is associated with fetal overgrowth. Knockout models involving the IGF-1 receptor demonstrate its importance in fetal growth and the importance of IGF-1 and IGF-2 action during fetal growth.

Table 6.1 lists important growth regulating genes and the impact that disruption or overexpression of these genes has on growth. Fig. 6.3 illustrates the impact of the GH-IGF axis on growth during fetal life, childhood and pubertal development.[3]

This figure incorporates the evidence from mouse models and mutations identified in humans. This large body of evidence demonstrates the pivotal role for the GH-IGF axis in the determination of growth throughout the lifespan. IGF-1 and IGFBP-3 levels increase

Table 6.1: Impact of gene deletion/overexpression on fetal growth.

Disruption of gene	Effect
IGF-1	Restrict fetal growth
IGF-2	Restrict fetal growth
IGF-1R	Restrict fetal growth
PAPP-A	Restrict fetal growth
IGF2R	Overgrowth
Overexpression of gene	**Effect**
IGF-2	Overgrowth

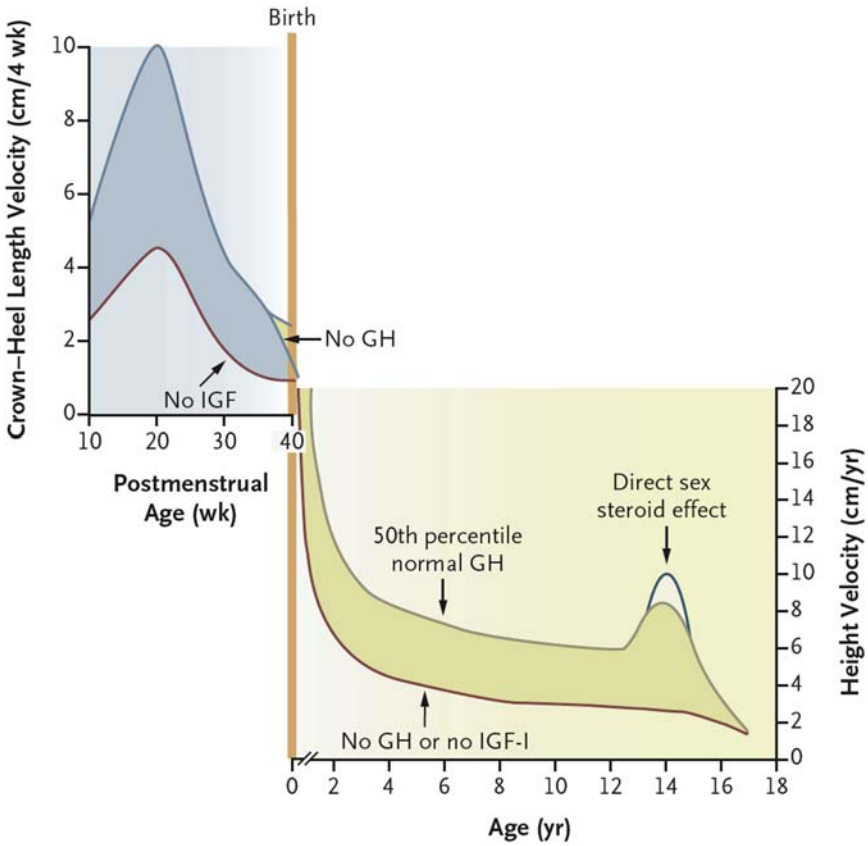


Fig. 6.3

Role of growth factors on growth velocity: *in utero* and postnatal.

cm, centimeter; *GH*, growth hormone; *IGF*, insulin-like growth factor; *wk*, week; *yr*, year.

from low levels at the time of delivery to a peak during pubertal growth spurt and then diminish slowly over time through adulthood. The levels of IGF-1 and IGFBP-3 in the blood paralleled changes in GH secretion and parallel linear growth.

Although GH and IGF-1 are considered to be the primary endocrine regulators of linear growth, other hormones also play a role. For example, elevated levels of insulin in children with severe obesity may help to drive linear growth. This may occur through insulin's action on the insulin receptor or cross-reactivity with the IGF-1 receptor. In addition, estrogen and testosterone have linear growth promoting effects that likely include GH-dependent and independent actions. During puberty, sex hormones increase the amplitude and frequency of growth hormone secretory pulses. Similarly, at the growth plate, sex hormones regulate growth and differentiation of chondrocytes ultimately promoting epiphyseal fusion. The endocrine impact of sex hormones on linear growth is dependent upon the timing of puberty. In fact, a significant reason for the adult height difference between sexes is the earlier pubertal development of males. In addition to GH deficiency (GHD), there are several other endocrine conditions that can have a pathological impact on growth. These include precocious puberty, acromegaly (gigantism) and hypogonadism. Although precocious puberty may cause growth acceleration, it also causes maturation of the growth plates leading to premature growth plate closure and cessation of linear growth. In individuals with peripheral precocious puberty, such as McCune-Albright syndrome, it may be difficult to slow the growth plate closure. Treatments to reduce sex steroid production or the impact of sex steroid on growth plate closure may be beneficial. In children with central precocious puberty, GnRH analog therapy to suppress gonadotropin production may be beneficial in allowing children to reach a normal adult height. Acromegaly (gigantism) is a rare condition in children caused by hypersecretion of GH by a pituitary adenoma. This condition is treated by surgical resection of the adenoma or with therapies to reduce GH production of the adenoma. Hypogonadism, due to primary gonadal failure or gonadotropin deficiency, leads to impaired linear growth without hormone replacement. However, replacement of sex steroids can lead to appropriate pubertal growth spurt. The timing of sex steroid replacement may be important to achieve maximal linear growth, with early replacement of low doses increasing over time to match the physiologic changes during puberty likely to result in the best growth outcome.

Another hormone that has been recently postulated to be associated with linear growth is C-natriuretic peptide (CNP). Levels of CNP and its precursor have been demonstrated to increase during periods of rapid growth, increase in response to GH therapy and reduce during periods of slow growth. CNP regulates linear growth at the level of the growth plate.

There are numerous regulators of growth at the level of the growth plate.[5,6] These include autocrine, paracrine and endocrine regulation. The action of these hormones regulate the activation and migration of the resting chondrocytes into the proliferative zone, the proliferation of chondrocytes in the proliferative zone, the hypertrophy of the chondrocytes in the hypertrophic zone and the differentiation of chondrocytes into bone at the leading edge of the growth plate. There are numerous hormones and their receptors involved in this regulation. Natriuretic Peptide Receptor-B (NPR-B) is the growth plate receptor for CNP. Inactivating mutations in the NPR-B receptor impair linear growth at the growth plate and result in acromesomelic dwarfism Maroteux type, a skeletal dysplasia with severe short stature. Activating mutations of the NPR-B receptor increase linear growth at the growth plate leading to tall stature. Children with idiopathic short stature (ISS) have been identified as having mild inactivating mutations in the NPR-B receptor. This spectrum of impact on linear growth has been demonstrated in several genes regulating proliferation and differentiation of the epiphyseal chondrocytes. Activating mutations in genes promoting proliferation lead to tall stature while inactivating mutations lead to either mild short stature or severe short stature and skeletal dysplasia. Similarly, activating mutations in genes promoting differentiation of epiphyseal chondrocytes can inhibit linear growth leading to short stature with or without skeletal dysplasia. Impairment of growth due to genetic abnormalities of genes regulating epiphyseal chondrocyte function should be considered primary growth disorders. The endocrine action of CNP is emphasized by the current development of CNP analogs for treatment of growth disorders including achondroplasia (Fig. 6.4).[7] Achondroplasia, the most common skeletal dysplasia, is caused by activating mutations in the fibroblast growth factor receptor 3 (FGFR3) that inhibit linear growth at the growth plate by promoting differentiation of epiphyseal chondrocytes. CNP analogs in current development include vosoritide and TransCon CNP. Treatment of children with achondroplasia using CNP analogs improve growth at the growth plate by bypassing the growth inhibiting effects of activating mutations of the FGFR3 mutation. A recent phase 3 clinical trial and phase 2 extension study have shown prolonged improvement in the linear growth of children with achondroplasia receiving vosoritide (a gain of 1.6 cm in one year compared to placebo or 5.7 cm over 3.5 years compared to natural history). Treatment with CNP analogs has been well tolerated. Current studies are underway for the use of CNP analogs and other forms of non-GHD growth impairment including SHOX deficiency, Rasopathies, and NPR-B mutations. In the future, CNP analog therapy may also be considered for children with Turner syndrome, other forms of mild growth impairment and ISS. CNP analog therapy may also be beneficial in other skeletal dysplasias. However, the mechanism of cause for each skeletal dysplasia will determine whether CNP analog therapy may be beneficial. Since activating mutations of the NPR-B receptor lead to disproportionate tall stature, it will be important to monitor for disproportion and skeletal complications of therapy with CNP analogs.

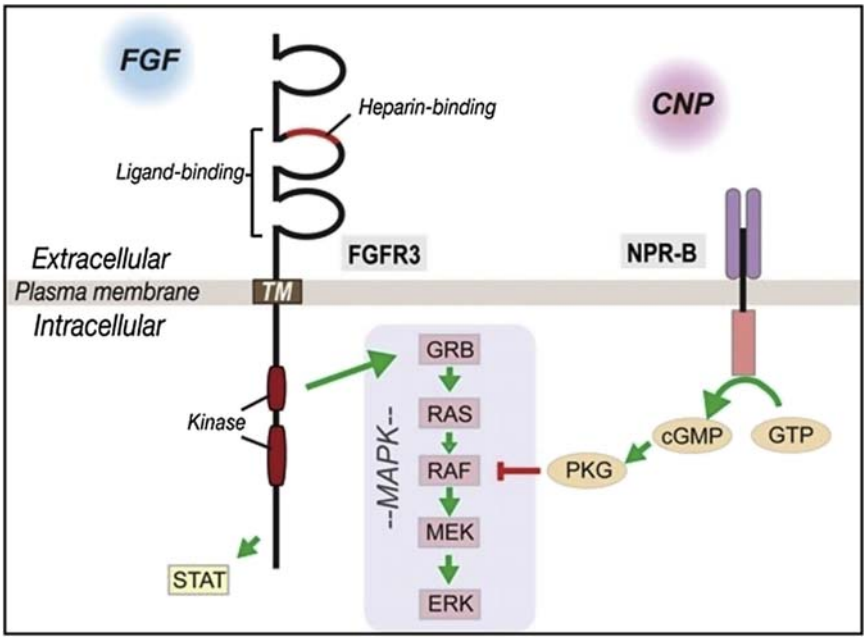


Fig. 6.4
C-natriuretic peptide analogue therapy in achondroplasia.
cGMP, cyclic guanosine monophophate; *CNP*, C-natriuretic peptide; *ERK*, extracellular signal regulated kinase; *FGF*, fibroblast growth factor; *FRFR3*, fibroblast growth factor receptor 3; *GRB*, growth factor receptor-bound protein; *GTP*, guanosine triphosphate; *MAPK*, mitogen-activated protein kinase; *MEK*, MAPK kinase; *NPR-B*, natriuretic peptide receptor B; *PKG*, protein kinase G; *RAF*, c-RAF proto-oncogene serine/threonine-protein kinase; *RAS*, c-Ras proto-oncogene GTPase; *STAT*, signal transducer and activator of transcription; *TM*, transmembrane.

Growth disorders characteristics, diagnosis and treatment

Short children may be classified into three separate groups.[8] Short normal children include two subgroups. The first subgroup is characterized by growth along a lower percentile with a normal growth velocity. Commonly, one parent has a height at a similar lower percentile. The second group includes children with short stature who have normal growth velocity during childhood years but have growth deceleration related to late onset of puberty and delayed pubertal growth spurt. Skeletal maturation may be delayed as early as the preschool years but more commonly becomes delayed in the peripubertal timeframe. Children with constitutional delay of growth and puberty tend to reach a height that is slightly below the mid-parental target height.

Second group of children with short stature are due to an early event. This early event may include *in utero* growth retardation, but may also represent an early event during the postnatal period. This includes premature birth. Although growth in the first 6 months of

life is independent of GH action and is largely dependent upon nutrition poor nutritional intake and chronic illness have a large and long-lasting effect on growth. Children during the first 2 years of life and demonstrate phenomenal catch-up growth, as has been described in international adoptees with psychosocial growth deprivation who demonstrate rapid catch-up growth in the first 6−18 months following adoption. However, if catch-up growth does not occur during this crucial time frame, it is more difficult to demonstrate catch-up growth at older ages to overcome growth failure in your life. Therefore, stature loss at this age is not easily recovered.

The last group of children with short stature includes a low growth velocity due to an identifiable and treatable cause.[6,9] Because of growth failure in this group includes a wide spectrum of disease and malnutrition. Once an explanation for the poor growth rate is identified and appropriate treatment recommended, catch-up growth can occur. A careful history, physical examination and laboratory investigation may identify the cause. This may require testing of the gamut of systems involving renal, gastrointestinal, cardiac, respiratory, hematologic and neurologic systems. In addition, careful attention needs to be paid to the social and family history as social deprivation can lead to psychosocial dwarfism and genetic conditions can lead to growth failure.

Growth disorders include numerous chronic conditions that can impair growth leading to secondary growth failure. These conditions include chronic inflammation that slows growth at the growth plate and can reduce GH production centrally and the production of IGF-1 at the liver. In the setting of inadequate nutrition, GH production is elevated due to its role in mobilizing lipids from fatty acid stores. However, IGF-1 production at the liver is reduced. This leads to growth impairment during states of inadequate nutrition. Inadequate nutrition and chronic inflammation may also delay progression into puberty. Leptin, a marker of fat reserve, is known to regulate pubertal development. Therefore, leptin deficiency in periods of low nutrition may impact pubertal development. GH and IGF-1 have been described as permissive factors for pubertal development. In fact, children with GH and IGF-1 deficiency frequently have delayed puberty. When GH is replaced, puberty tends to progress at an appropriate rate, though there is speculation that high doses of GH therapy may encourage puberty to move faster and the growth plates to mature faster.

There are numerous medications that can impact the endocrine system leading to a negative impact on growth. Glucocorticoid therapy has been shown to impair growth by reducing GH secretion from the pituitary gland, reducing IGF-1 production of the liver and impairing the response of the growth plate to both GH and IGF-1. This powerful triple negative effect of glucocorticoids on growth is seen in the growth impairment of exogenous glucocorticoid therapy as well as endogenous glucocorticoid production in the setting of Cushing's disease or Cushing's syndrome.

Stimulant medications to treat attention deficit and hyperactivity disorder (ADHD) have been postulated to impair linear growth through reduction in nutrition. There is conflicting evidence as to whether these treatments have a long-term negative impact on growth. In one set of studies, no impairment in adult height was seen in children with ADHD receiving stimulant therapy. However, in another group of studies from the University of California-Irvine showed that long-term stimulant therapy impaired adult height by approximately 1 inch. However, most parents of children with ADHD would agree that the life-changing benefits of stimulant therapy would outweigh the small negative impact on adult height. However, there may be some children who have a larger negative impact of ADHD stimulant therapy on their linear growth. The precise mechanism of impairment of linear growth in children receiving stimulant therapy for ADHD remains unclear. Children with ADHD have also been shown to grow less than expected in response to GH therapy whether they are receiving stimulant therapy or not. Therefore, the hyperactivity associated with ADHD may have some impact on overall linear growth and the linear growth response to GH therapy.

Retinoic acid used for chemotherapy of childhood cancer and treatment of severe acne causes premature differentiation of the chondrocytes in the growth plate leading to an advanced bone age. This can lead to premature growth plate closure. Although this is not an endocrine effect, it is an important impact on growth that providers need to be aware of.

Thyroid hormone regulates GH production. In children with severe hypothyroidism, growth deceleration occurs due to decrease GH production. In this setting, the skeletal maturation as represented by bone age is typically delayed. Very high levels of thyroid stimulating hormone (TSH) may cross-react at the luteinizing hormone receptor and cause early pubertal development. Following thyroid hormone replacement, catch-up growth is noticeable within 6 months of treatment. If severe hypothyroidism occurs in children during the peripubertal or pubertal time, there may be an adequate time for catch-up growth before the growth plates close. In this setting, delay of pubertal progress using gonadotropin releasing hormone (GnRH) agonist therapy may be considered to allow children to have adequate time for catch-up growth. Following severe hypothyroidism, some children develop GHD. This may be due to enlargement of the pituitary cells producing TSH (thyrotropes) that impair or impinge upon the adjacent GH-producing cells (somatropes or somatomammotropes). Magnetic Resonance Imaging (MRI) of the pituitary in individuals with severe hypothyroidism has demonstrated enlargement of the pituitary gland likely due to overgrowth of the thyrotropes. This can lead to impairment of the catch-up growth process resulting in impaired adult height. Therefore, it is important to monitor for normalization of growth factors after thyroid hormone replacement in severe hypothyroidism, particularly in older children. If the growth factors do not normalize as the thyroid hormone replacement normalizes TSH, testing for GHD should be considered.

Following cytotoxic chemotherapy for childhood cancer, many children develop partial or complete gonadal failure. In those children, the pattern of gonadotropin secretion differs. Instead of having slow progression into and through puberty, they rapidly move through pubertal development and run out of time to grow earlier than usual. In the typical child entering puberty, pulses of gonadotropins are small and infrequent with the amplitude and frequency of the pulses increasing as puberty progresses. However, in children with gonadal damage, the impaired feedback loop leads to earlier and more intense increases in the amplitude and frequency of pulses of gonadotropins. In addition, as the gonad fails, the reduced production of sex steroid (testosterone or estrogen) limits the sex steroid stimulated growth through GH-dependent and independent pathways. Unfortunately, the early and rapid production of sex steroids leads to growth plate maturation that is continued despite relative sex steroid deficiency and ultimately leads to premature epiphyseal closure. Therefore, it is important to monitor childhood cancer survivors for early entry into puberty and rapid pubertal progress during puberty. In male childhood cancer survivors, testicular volume is not an accurate indicator of pubertal progress due to damage to germ cells that make up the majority of the testicular size increase during puberty. Therefore, hormonal testing and bone age monitoring should be initiated early in childhood cancer survivors. It would be appropriate to begin monitoring at the earliest normal time which children typically enter puberty (8 years for girls and 9 years for boys). In childhood cancer survivors who have received cranial radiation, particularly high doses, and in children who have received intrathecal methotrexate, the risk of GHD is increased. Therefore, monitoring growth factors following these cancer treatments is important. Growth deceleration may be a key sign of developing GHD in these children. However, children entering puberty early may maintain their growth on a normal curve due to the pubertal development while masking the growth deceleration associated with GHD. Neurosecretory GH dysfunction encompasses reduced GH secretion due to hypothalamic or pituitary impairment and may be difficult to diagnose with GH stimulation testing.

Numerous defects in the GH-IGF-1 axis have been identified as potential causes of growth impairment. First, abnormalities of development of the hypothalamus and pituitary gland can cause congenital GH deficiency (GHD) as well as other hormone deficiencies. Children with congenital GHD may have mildly impaired linear growth at birth and demonstrate growth failure usually after the first 6 months of life. However, in the more severe cases, growth failure may be identified earlier. Even in the absence of other pituitary hormone deficiencies, severe GHD can lead to hypoglycemia in the infant. In this situation, GH replacement therapy can be lifesaving. Milder forms of anatomic abnormalities of the pituitary gland, including ectopic posterior pituitary, may be associated with organic GHD and other pituitary deficiencies. Due to their milder nature, these forms of GHD may be identified in younger children but not infancy. Milder forms of GHD are typically identified by growth deceleration in otherwise healthy children.

Although GHD is rare, being identified in 1 and 200 children growing below the third percentile for an incidence of approximately 1 and 3500 children, it should be suspected in children who are demonstrating growth deceleration, growing steadily below the normal curve, or growing significantly below the mid-parental target height expected for their family. Screening tests for GHD include serum levels of IGF-1 and IGFBP-3. IGFBP-3 is more sensitive in children less than 3. IGF-1 values below -1 SDS are suggestive of GHD in older children though less specific in children less than the age of 3 years. In peripubertal children, the IGF-1 levels may dip as they approach their pubertal growth spurt. Therefore, in children with constitutional delay of growth and puberty, GHD may be suspected and diagnosed, but this may be a transient GH problem that is more physiologic than pathologic. Once the onset of puberty occurs, estrogen and testosterone production leads to increased GH production resulting in normal IGF-1 and IGFBP-3 levels and an appropriate pubertal growth spurt.

GHD is identified by the combination of auxological and biochemical factors including growth failure, low or low normal growth factors, abnormal pituitary imaging and/or abnormal results on GH stimulation testing. IGF-1 and IGFBP-3 are useful screening tools for the diagnosis of GHD. However, since IGF-1 levels are relatively low in the first few postnatal years, low IGF-1 levels are less specific for GHD in children less than 3 years. Low levels of IGFBP-3 are more predictive of GHD in children less than 3 years than IGF-1. There are several pitfalls of using IGF-1 and IGFBP-3 as screening tests for growth failure. In children with chronic renal insufficiency, there are increased levels of IGFBP-3 proteolysis leading to falsely high values of IGFBP-3 on blood testing. These false values occur because the immunoassay for IGFBP-3 recognizes the proteolytic fragments. In children with chronic renal insufficiency, IGF-1 levels are also falsely elevated. In children born Small for Gestational Age (SGA) without adequate catch-up growth, and several conditions associated with intrauterine growth retardation, IGF-1 and IGFBP-3 levels may be elevated due to the degree of IGF receptor resistance. This pattern is particularly notable in children with Russell-Silver syndrome.

GH stimulation testing involves a group of pharmacological interventions intended to promote the release of GH. Since GH production is suppressed by food, it is important that a GH stimulation test be performed while a child is fasting. There are numerous agents that have been developed alone and in combinations to promote GH release. The gold standard is considered to be insulin-induced hypoglycemia. However, this is infrequently used in children due to potential safety concerns. Other GH stimulating agents include clonidine, arginine, L-dopa, GH releasing hormone, glucagon, macimorelin and others. The thresholds for determining GHD using GH stimulation test depend upon the GH assay that is used and the local cutoff values. In the US, a peak GH value less than 10 ng/mL has been considered diagnostic of GHD in children. The values differ for adults. In addition, some GH stimulatory agents are not effective for use in adults.

Due to the relative GHD that occurs in peripubertal children, sex steroid priming has been recommended in this population to reduce the number of children diagnosed with GHD. Sex steroid priming involves administration of low-dose estrogen or testosterone prior to GH stimulation testing. When priming is utilized, fewer children have GH peaks categorized in the deficient range. However, there is no longitudinal data to demonstrate that those children who had a normal GH stimulation peak following sex steroid priming have normal linear growth and GH production leading to a normal adult height. Therefore, to validate the utility of sex steroid priming in peripubertal children long-term follow-up data is needed to demonstrate that children with GHD are not missed by this pharmacological manipulation of the GH response to stimulation. Although sex steroid priming is typically well-tolerated, side effects can include breast growth and tenderness after estrogen treatment or priapism after testosterone treatment.

The causes of GHD include congenital and acquired causes. The congenital causes are associated with genetic defects, structural defects of the brain and midline facial defects. The acquired causes include trauma, infection and intracranial tumors. The association of GHD with perinatal trauma or hypoxia is controversial and may require prolonged hypoxemia. A traumatic delivery, would not be expected to impact pituitary or hypothalamic function due to their location in the brain. Hypoxic injury to the pituitary and hypothalamus would not be expected unless there is evidence of hypoxic damage to other, more oxygen sensitive regions such as the occipital neurons. Postnatal trauma, including recurrent concussion and traumatic brain injury may be associated with varying degrees of GHD. Infectious causes of GHD include meningitis and encephalitis and depend upon the regions affected. GHD related to central nervous system tumors is typically related to the location of the tumors and is associated with craniopharyngioma, germinoma involving the pituitary and/or pituitary stalk (infundibulum) and histiocytosis which also has a propensity for the pituitary stalk. GHD may also occur after pituitary infarction. Transient forms of GHD include the relative decrease in GH secretion in the peripubertal time, reversible GHD due to severe hypothyroidism and impaired GH secretion in children with psychosocial deprivation.

There are numerous genetic conditions associated with GHD, primarily related to abnormalities of pituitary function and development.[10] In addition, there are numerous abnormalities in the GH-IGF-1 cascade.[5] Abnormalities in GH include GH gene deletions that impact production and function of GH. Abnormalities in the GH receptor gene involve the extracellular, transmembrane and intracellular portions of the receptor. Individuals with abnormalities of the GH receptor have GH resistance and a clinical phenotype denoted as Laron syndrome. Individuals with GH resistance typically have very high peaks on GH stimulation testing associated with low levels of IGF-1 and IGFBP-3. In addition, in response to a GH challenge (IGF production test), they have very low IGF-1 or IGFBP-3 production. Other forms of GH resistance include abnormalities in post receptor signaling including

mutations in Stat5b. Individuals with mutations in Stat5b have a Laron-like syndrome with GH resistance that is also associated with immune deficiency. Other abnormalities in the GH-IGF-1 axis include abnormalities in the IGF-1 molecule. Mutations in the ALS have been shown to be associated with growth failure and pubertal delay. The clinical profile of a child with an ALS defect would include low levels of IGF-1 and IGFBP-3 with normal GH stimulation testing or evidence of elevated GH levels. Although the IGF binding proteins are a crucial component in the delivery of IGF-1 to the target tissue, no abnormalities have been identified in humans related to abnormal IGFBP-3. This is likely because IGFBP-5, though present at smaller levels in the serum, has similar IGF-binding and delivery characteristics to IGFBP-3. This redundancy likely prevents any phenotype of IGFBP-3 deficiency. Abnormalities in the IGFBP-3 protease, PAPP-A2, have been demonstrated to impair growth by impairing release of IGF-1 to the target tissue. Individuals with abnormalities in the IGF-I receptor have been identified. These individuals have typically had elevated levels of IGF 1 as a clinical indicator of this IGF resistance. However, children were born small for gestational age (SGA) without catch-up growth also frequently demonstrate some degree of IGF-1 resistance. Abnormalities in the IGF receptor signaling cascade can also lead to growth impairment. This includes the group of conditions known as Rasopathies. The Rasopathies include Noonan syndrome, cardiofaciocutaneous syndrome, Costello syndrome and neurofibromatosis type 1. Since the Ras pathway is important in translating the proliferative action of the IGF-1 receptor at the target tissue, children with these conditions can have impaired growth and impaired response to GH therapy requiring higher doses of GH to improve linear growth. Children with Noonan syndrome, in particular, have responded to GH therapy with improved linear growth and improved adult height. Notably, early studies of GH therapy in Noonan syndrome with low doses did not show significant benefit. However, later studies with higher GH doses showed significant linear growth benefit and improved adult height.

Growth hormone therapy

Since 1985, GH therapy has been available as a subcutaneous injection of recombinant human GH given either daily or 6 days/week. Attempts at developing long-acting preparations of GH (LAGH) have occurred since 1979 beginning with a gel preparation and followed by multiple different mechanisms of prolonging GH action and availability.[11] In 1999, Nutropin Depot® was approved by the US Food and Drug Administration (FDA) for treatment of children with GHD. However, in 2003, Nutropin Depot® was removed from the market citing manufacturing difficulties. Since then, numerous attempts have been made to develop a LAGH. Currently, there are three preparations of LAGH approved for use in different countries around the world. Sogroya®, somapacitan, is a GH molecule that has been modified to include an acyl linker that improves binding to endogenous albumin. The use of a similar acyl linker technology has been successfully used in other FDA-approved

therapeutic agents including liraglutide, insulin detemir, insulin degludec and semaglutide. Sogroya® was FDA-approved in August 2020 for the treatment of adult GHD. However, it is not yet commercially available. Sogroya® is currently being studied as a once weekly injection in a phase 3 clinical trial for pediatric GHD and a phase 2 clinical trial for children with short stature due to being SGA without adequate catch-up growth. TransCon™ hGH (lonapegsomatropin) completed a phase 3 clinical trial in children with GHD demonstrating statistically superior linear growth over 12 months compared to daily Genotropin®. TransCon™ hGH is a prodrug with native GH (22 kDa) transiently conjugated to a 40 kDa polyethylene glycol carrier by a transient linker that is cleaved at physiologic pH and temperature at a consistent rate. Cleavage of the prodrug allows delivery of native GH into the circulation at a consistent rate following a weekly injection. Somatrogon© is an engineered GH with the addition of 3 C-terminal peptide (CTP) cartridges to the GH molecule. These CTP cartridges represent a portion of the C-terminal end of naturally occurring human chorionic gonadotropin (hCG) that conveys a longer half-life of hCG compared to luteinizing hormone. The addition of this 3 CTP cartridges to the native 22 kDa GH molecule results in a 66 kDa molecule. Somatrogon© completed a phase 3 clinical trial as a once weekly injection in children with GHD demonstrating numerically superior linear growth over 12 months compared to daily Genotropin®. Pending FDA-approval, TransCon™ hGH and Somatrogon© LAGH molecules are likely to be available for commercial therapy of pediatric GHD beginning in mid to late 2021. Although once weekly GH therapy is expected to improve the linear growth response due to improved adherence, this remains to be shown in clinical practice. Unfortunately, adherence will still be impacted by the fatigue associated with regular injections, social and psychological factors. However, if adherence is improved, it is my hope that LAGH therapy will not only be non-inferior to daily GH therapy but will lead to improved linear growth and body composition responses to LAGH treatment on a long-term basis.

In addition to daily GH and LAGH therapy, GH secretagogues have been studied for the potential improvement of GH production in children and adults. An orally bioavailable analog of GH releasing peptide (GHRP) 6, LUM−201 (also known as ibutamoren mesylate or MK-677), is currently being studied in children with GHD. In previous studies, LUM 201 has been shown to improve the pulsatile production of GH by stimulating the GH secretagogue receptor, also known as the ghrelin receptor. LUM-201 would only be effective in individuals who have pituitary tissue responsive to treatment. However, this compound promises to be an effective daily oral agent for increasing linear growth due to increased GH production in those children able to respond. The fact that LUM-210 can be delivered as an oral pill is a significant advance in the treatment of children with GHD who currently require a daily injection and may even be considered favorable compared to once weekly injections. Repeated administration of GHRP6 has been shown to desensitize its stimulatory effect on GH secretion. Therefore, long-term

studies of LUM-201 are necessary to demonstrate a persistent ability to improve the amplitude of GH pulsatile production, increase IGF-1 and IGFBP-3 and resulting linear growth.

During GH therapy, IGF-1 monitoring has been used to improve linear growth response and for safety. It is recommended that IGF-1 levels be targeted within the normal range (between −2 and +2 SDS). Dosing of GH based upon IGF-1 targets to +2 SDS has shown improved linear growth in the first year of therapy, however, long-term outcomes of IGF-1-based dosing have not been published. Therefore it remains unclear whether targeting an IGF-1 to the upper part of the normal range improves adult height. Clinical trial studying IGF based dosing demonstrated that a 20% increase or reduction of the GH dose is likely to increase or reduce the IGF-1 standard deviation score by approximately 1 standard deviation. However, these clinical trials also demonstrated a wide range of sensitivity to GH. In fact, children received a wide range of doses to achieve an IGF-1 at 0 or +2 SDS. In order to achieve an IGF-1 of +2 SDS some children required doses as high as 2 mg/kg/week. Such doses are considered to be extremely supraphysiologic. More recently, it has been recommended that IGF-1 values be targeted to the mean or +1 SDS. In childhood cancer survivors, it is recommended that the IGF-1 be targeted between −1 and 0 SDS. However, there is no clear evidence that higher IGF-1 levels within the normal range or above +2 SDS are related to an increase in adverse events related to GH therapy or long-term safety of GH therapy. Regardless, it is felt to be prudent to maintain IGF-I levels in the physiologic replacement range between −2 and +2 SDS unless the clinical circumstances dictate otherwise.

There are several pitfalls of using IGF-1 and IGFBP-3 as monitoring guidance for GH therapy. As described previously, children with chronic renal insufficiency, have falsely elevated levels of IGF-1 and IGFBP-3. However, GH therapy has been shown to be beneficial to improve linear growth of children with chronic renal impairment. It is likely that this growth promoting effect is due to increased action of GH at the target tissue including stimulation of resting chondrocytes into the proliferative zone and improved local production of IGF-1 at the growth plate. Monitoring IGF-1 and IGFBP-3 levels in most children with chronic renal insufficiency is not useful in guiding dose adjustment. During GH therapy, children with Russell-Silver syndrome frequently have very elevated IGF-1 and IGFBP-3 levels. However, if the dose of GH is reduced the linear growth benefit disappears. Therefore, continued GH therapy at a conservative dose (such as 0.25 mg/kg/week; 35 mcg/kg/day) is recommended despite these growth factor elevations. In children with Prader-Willi syndrome, similar elevations of growth factors in response to GH therapy have been observed. Again, continuing GH therapy at a conservative dose (such as 0.25 mg/kg/week or 1 mg/m^2/day) is recommended despite these growth factor elevations. In children with Prader-Willi syndrome, the elevated growth factor levels are

particularly seen in young children or as children are becoming more obese. This pattern correlates to high IGF-1 levels seen in obese children in general. It is interesting that these conditions with elevated growth factor levels prior to and in response to GH therapy involve conditions associated with methylation defects. This leads to speculation that regulation of growth factor levels may also be regulated by a methylation-dependent mechanism.

Assessment of growth in clinical scenarios

The definition of short stature is arbitrarily assigned based upon the normal distribution of height in a population. Children with short stature are described as those below the third percentile (<−2.0 SDS). Using this definition, 3% of children will naturally be considered to have short stature regardless of any pathology. It is also important to note that stature varies depending upon the ethnic background of individuals. As such, reference charts exist for multiple populations around the globe. There have been clear secular trends in increasing height documented in Europe over the last 50 years. Based upon the secular trends, each generation in the United Kingdom has been demonstrated to be 1−1.5 cm taller than the previous generation. For additional information on growth, maturity and growth references and standards in Chapters 11, 12 and 14.

"The rate of a child's growth in height follows an extraordinarily regular path; so much so, in fact, that rate of growth is one of the best indices of a child's general health (James Mourilyan Tanner, 1981)." This idiom is used in clinical practice in the monitoring of the child's growth. Typically, children will find a channel in which their growth will track over time. This pattern is termed growth canalization. If the child has growth acceleration or deceleration sufficient to cross isopleths into a different canal of the growth chart this may represent pathological growth. However, there are several ages in which crossing those growth channels may be normal. For example, in the postnatal period, growth may decelerate to a height percentile that is more appropriate for the genetic potential of the child. Following the growth spurt in the infant, growth deceleration may also occur for similar reasons, particularly in children destined to have constitutional delay of growth and puberty. Children with early normal puberty will have apparent growth acceleration compared to their peers. Children with late normal or delayed puberty will appear to have growth deceleration compared to their peers who have entered puberty at a normal time. Growth velocity curves have also been utilized to establish normal growth in children. However, due to the pulsatile nature of growth in children, the growth velocity does not typically follow a similar pattern of canalization.

Fig. 6.5 shows the CDC 2003 height and weight growth reference curves for boys.[12] This reference, and the height and weight reference curves for girls and BMI reference curves for both sexes, was developed using cross-sectional data representing thousands of

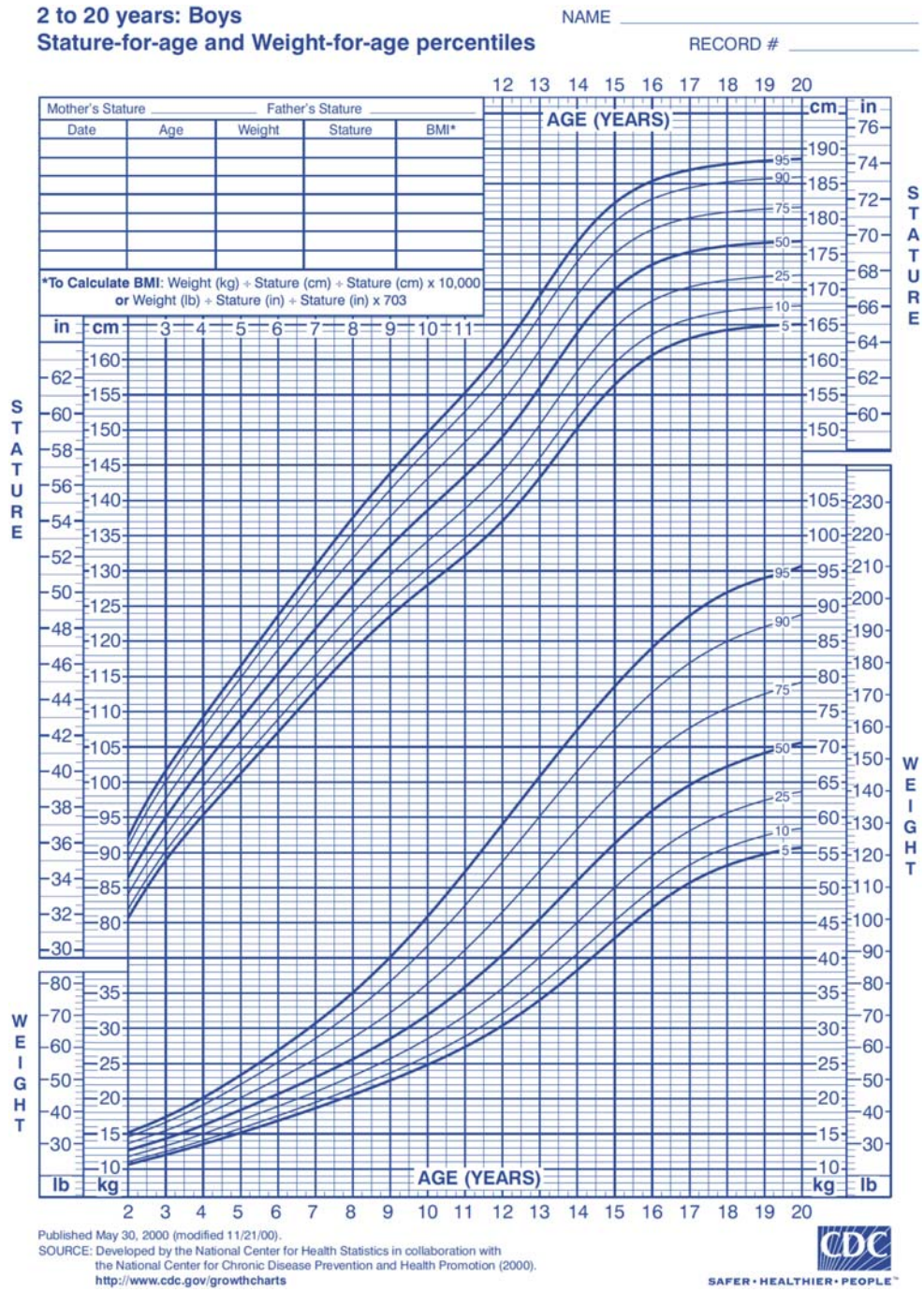
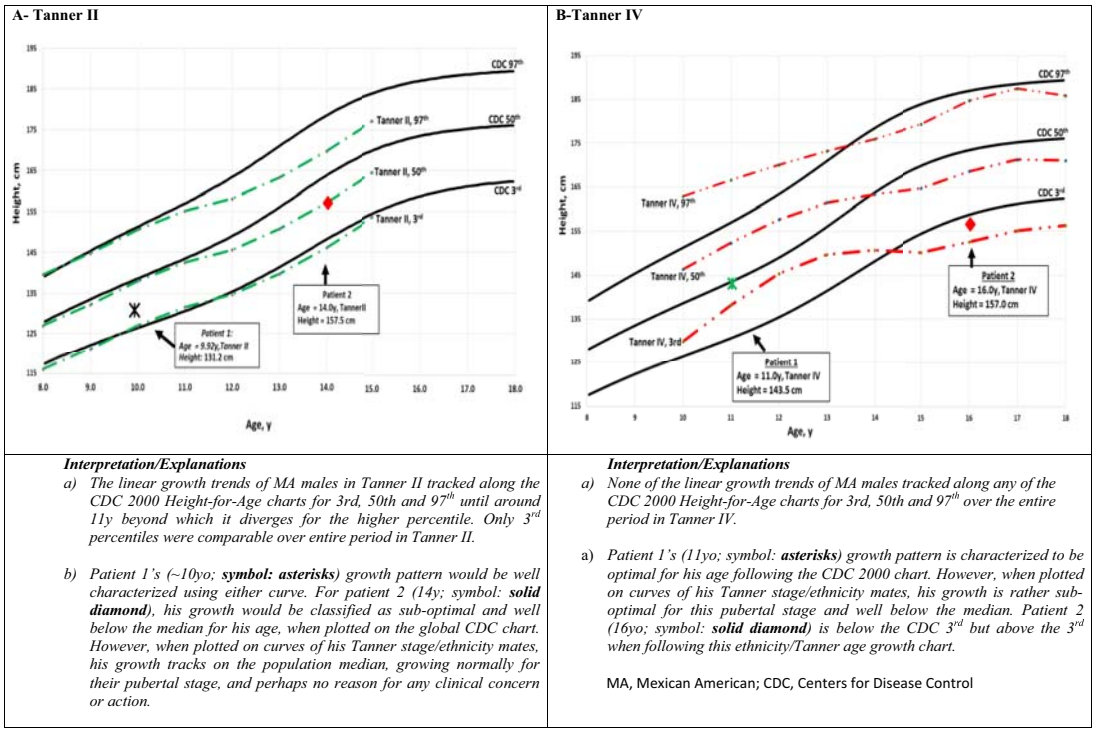


Fig. 6.5
CDC growth curve: 2–20 years: boys stature weight-for-age percentiles.

children across multiple ethnic groups representative of the US population. Unfortunately, few longitudinal cohorts are available to demonstrate appropriate longitudinal growth. As described above, there are multiple times when healthy children will diverge from this population growth pattern. Thus, it is important to use clinical judgment when interpreting growth patterns in children. Children with early normal pubertal development can be considered tall for their age and classified as overweight due to their large muscle mass. In contrast, children with late normal pubertal development may be considered to have growth deceleration, be short for their age or underweight. However, when the growth curve is adjusted for pubertal status, children are more likely to be classified appropriately. Since there are significant differences in the timing of pubertal development based upon ethnicity, the ethnicity also needs to be incorporated in this evaluation. Reference curves have been developed based upon the United States National Health and Nutrition Examination Survey which included pubertal status.[13] The use of these Tanner Stage Adjusted reference curves may help clinicians more appropriately classify children based upon their growth and pubertal status (Fig. 6.6).



Interpretation/Explanations

a) The linear growth trends of MA males in Tanner II tracked along the CDC 2000 Height-for-Age charts for 3rd, 50th and 97th until around 11y beyond which it diverges for the higher percentile. Only 3rd percentiles were comparable over entire period in Tanner II.

*b) Patient 1's (~10yo; **symbol: asterisks**) growth pattern would be well characterized using either curve. For patient 2 (14y; symbol: **solid diamond**), his growth would be classified as sub-optimal and well below the median for his age, when plotted on the global CDC chart. However, when plotted on curves of his Tanner stage/ethnicity mates, his growth tracks on the population median, growing normally for their pubertal stage, and perhaps no reason for any clinical concern or action.*

Interpretation/Explanations

a) None of the linear growth trends of MA males tracked along any of the CDC 2000 Height-for-Age charts for 3rd, 50th and 97th over the entire period in Tanner IV.

a) *Patient 1's (11yo; symbol: **asterisks**) growth pattern is characterized to be optimal for his age following the CDC 2000 chart. However, when plotted on curves of his Tanner stage/ethnicity mates, his growth is rather sub-optimal for this pubertal stage and well below the median. Patient 2 (16yo; symbol: **solid diamond**) is below the CDC 3rd but above the 3rd when following this ethnicity/Tanner age growth chart.*

MA, Mexican American; CDC, Centers for Disease Control

Fig. 6.6
A sample Tanner stage height-for-age curves for Mexican American males superimposed on the CDC 2000 charts.

Parental heights are used to help estimate the genetic potential of a child. This is a useful comparison against which to judge the current height of a child. A standard formula used to calculate the mid-parental target height is to average the height of the parents and add 2.5 inches for boys and subtract 2.5 inches for girls. When this formula is used, approximately two-thirds of children will reach a height within 2 inches of their mid-parental target height and 97% will achieve a height within 4 inches of their mid-parental target height. If the child is growing at a height that is more than 2 standard deviations below the mid-parental target height, this increases the likelihood of an abnormality impacting growth that could be a chronic illness, malnutrition, a hormone deficiency or a genetic abnormality. Therefore, it is important to compare the growth of children to that expected by their estimated growth potential based upon the height of their parents. The shorter the child is compared to the general population or to the mid-parental target height, the more likely a pathologic cause of growth failure is to be identified.

When assessing linear growth over time, it is important to allow sufficient time between growth points. During infancy the time interval should be at least 3 months and during childhood and adolescence the best time interval would be at least 6 months. Shorter intervals of measurement run the risk of misinterpretation of values due to the degree of measurement error. A key error often occurs in interpreting growth as children transition from having a measurement of length to a measurement of height. This transition occurs between the ages of 2 and 3 years. Children and adults are longer than they are tall. Therefore, if they length is plotted on a height chart a child will look taller than they are. In contrast, if a height is plotted on a length curve the child will look shorter than they are. This error in interpretation during the transition between length and height measurements may lead to unnecessary clinical investigation of poor growth or delayed investigation of poor growth depending upon which error occurs.

In children who receive spinal radiation, they may have impaired growth of the spine leading to impaired statural growth. Therefore, monitoring of the growth children following spinal radiation may benefit from the use of measuring arm span, sitting height or upper to lower segment ratios.

There is a high correlation between heights measured at different ages. For this reason, there are rules of thumb that suggest that the height at 3 years of age can be used to predict the adult height. However, these rules of thumb do not apply to the growth pattern of many individuals. Since the heights of different ages strongly correlate, growth deceleration that is progressive over time also increases the likelihood of pathology. Therefore, if children show progressive deceleration over more than 1 year further growth evaluation should be considered.

One final point is that monitoring of growth over time is crucial. The majority of growth disorders should present by the time of school entry making growth surveillance programs

more effective in the preschool or early school years. However, further growth disorders may be recognized as late as puberty requiring continued close monitoring of growth. This is particularly important as the routine monitoring growth and the routine occurrence of well-child visits decreases in school-aged children. Therefore, some growth disorders are not identified until it is too late to intervene. There is also a significant bias in the recognition, referral and treatment of girls with short stature. In addition, there is also ethnic and social economic bias in the monitoring, recognition, and referral of children with short stature.

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CHAPTER 7

Nutrition and growth

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Introduction

Nutrition has been broadly defined as "the processes whereby cellular organelles, cells, tissues, organs, systems, and the body as a whole obtain and use necessary substances obtained from foods to maintain its structural and functional integrity".[1] "*Necessary* substances" may also be described as "*essential* nutrients" and the maintenance of structural and functional integrity as "life and health", making a useable definition "the provision of essential nutrients necessary to support human life and health".[2]

Regardless of where we live and the nutrients we select and consume, our body composition, the structure and chemical composition of our cells, tissues, and organs, are remarkably similar. The lean body mass typically consists of 72% water, 21% protein, 7% minerals, and less than 1% of carbohydrate and other nutrients. It follows that a wide range of diet types can satisfy nutritional needs and promote optimal growth within specific environments. For much of human evolution and for some (non-industrialized) groups today, the physical environment and climate determined what could/can be procured or cultivated. However, technology and the economic power to develop and exploit it allow us to inhabit the major landmasses of the planet and exploit their ability to provide adequate nutrients for human survival. National economic and socio-political factors are the major distal determinants influencing food choice and sufficiency, but at the community and family level local socio-economic factors including income, housing, health care, sanitation, and education (primarily maternal) are proximal determinants of food sufficiency, nutritional intake, and adequate growth. So determining the adequacy of nutrient availability, and nutritional intake that allow normal growth to take place, is a complex process.

This chapter has the following aims:

- to discuss the basic concepts of nutritional science needed for an understanding of the relationship between nutrition and growth (nutrition vs. diet)
- to discuss nutritional requirements during infancy, childhood, and adolescence

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- to discuss the etiology and effect of malnutrition during growth, including nutritional deficiency and abundance (general and specific)
- to review the assessment of nutritional status and dietary intake in children

Basic concepts

Nutrition and diet

Nutrition and diet are not synonymous; the nutrients required for normal health and wellbeing are obtained through the diet. Clearly the availability of specific nutrients, and the ability to pre-process them prior to ingestion and digestion, will determine the breadth and suitability of the diet.

Nutrients

Nutrients are grouped as essential (indispensable) if they are only derived from the diet (i.e. there is no *de novo* synthesis or insufficient synthesis) or non-essential if they are synthesized from the diet or naturally present in the diet at levels in excess of need (e.g. dietary fiber). However, in certain circumstances (pregnancy, lactation, senescence) previously non-essential nutrients become "conditionally essential" because they need to be synthesized in greater amounts than normal to cope with the growth and development of the fetus.

The essential nutrients are listed in Table 7.1. All humans require the same essential nutrients, but in different amounts according to age, sex, activity levels, health status, the physical environment and, in the case of females of reproductive age, pregnancy.

In addition to classifying nutrients as essential and non-essential they can also be classified by the amount consumed as macronutrients, that are consumed in large quantities (e.g. in amounts of $\pm 10 \times$ g per day) and micronutrients consumed in smaller amounts (e.g. $\pm$ mg per day). There are also macro-minerals, such as calcium (Ca), sodium (Na), chloride (Cl), magnesium (Mg), and potassium (K), that are required in greater amounts than other micro-nutrients and trace elements such as chromium (Cr), boron (B), and molybdenum (Mo) (Table 7.1).

Essential macronutrients include carbohydrates, fats, and proteins and essential micronutrients include minerals and vitamins. The primary function of essential macronutrients is to provide energy (carbohydrates) and support growth and repair (fats and proteins). Micronutrients are more concerned with supporting metabolism by providing the essential chemicals for normal physiology, biochemical function, and homeostasis. In addition, minerals and vitamins are essential for normal growth and health as the occurrence of nutritional diseases, caused by mineral and vitamin deficiency,

Table 7.1: Essential nutrients of the human diet.

Carbohydrate	**Mineral**	**Vitamins**
Glucose	*Macronutrient elements*	*Fat-soluble*
	Calcium	A (retinol)
Fat or lipid	Phosphorous	D (cholecalciferol)
Linoleic acid	Sodium	E (Tocopherol)
Linolenic acid	Potassium	K
	Sulfur	*Water-soluble*
Protein	Chlorine	Thiamin
Amino acids	Magnesium	Riboflavin
Leucine	*Micronutrient elements*	Niacin
Isoleucine	Iron	Biotin
Lysine	Selenium	Folic acid
Methionine	Zinc	Vitamin B6 (pyridoxine)
Phenylalanine	Manganese	Vitamin B12 (cobalamin)
Threonine	Copper	Pantothenic acid
Tryptophan	Cobalt	Vitamin C (ascorbic acid)
Valine	Molybdenum	**Water**
Histidine	Iodine	
	Chromium	
	Vanadium	
	Tin	
	Nickel	
	Silicon	
	Boron	
	Arsenic	
	Fluorine	

demonstrates. The most common deficiencies include Iron deficiency anemia[3]; hypothyroidism from iodine deficiency[4]; rickets from a lack of Vitamin D[5]; Vitamin B12 deficiency leading to megaloblastic anemia[6,7]; Calcium deficiency as a primary cause of osteoporosis[8]; Vitamin A deficiency leading to blindness, and Magnesium deficiency implicated in over 300 enzyme reactions.[9]

Measurement of food and energy intake

There are regular surveys of diet and nutrition in many countries and frequent research reports on dietary intake and nutritional status at national, community, household, and individual levels. In the UK, for example, regular national surveys of diet and nutrition are undertaken to establish the nutritional standards across a variety of age and sex demographics.[10] However, several methodological issues need to be considered. The apparently simple task of collecting accurate, representative data of the food intake of people going about their everyday way of life is notoriously difficult, often requiring a compromise between practicality, precision, and accuracy.

Similarly, it is not difficult to find up to date government and institutional research reports that relate to the nutritional needs of the various demographic groups of the population by describing their net intake over time. However, the bases of these figures and their correct use are not straightforward and to make critical observations, assessments, and decisions on nutrition and growth, it is important to consider these intricacies.

The measurement of habitual food intake is an example of Heisenberg's uncertainty principle: the harder you try to measure something, the more likely you are to affect what you are trying to measure. The decisions made by individuals about the food they consume are sensitive to many subjective feelings and attitudes that may change depending on factors outside the influence of the researcher. Time of day, season of the year, available foods, social setting, proximity to previous or future exercise schedules, are just some of the factors that influence dietary intake. It is possible to perform accurate measurements, to less than 1% of the real value, of energy and nutrient intake in experimental conditions with the participants housed in environmentally controlled nutrition units and provided with their meals at set times. Duplicate meals and snacks are weighed and analyzed by accurate physical and chemical methods. (Of course, you can never analyze what someone has eaten because, if they have eaten it, you cannot analyze it, and if you have analyzed it, they cannot eat it). The problems of accurate measurement of intake arise when we wish to measure the habitual food intake of people in non-experimental conditions i.e. when they are leading their everyday lives. It is technically difficult and inconvenient to weigh the food consumed in many circumstances. This is particularly true when a meal is being cooked - does one weight the raw materials used to create the meal or the final meal itself? Also, the complete meal may not be eaten and so the remains must also the weighed. The inconvenience of weighing may influence the foods chosen or the number of meals and snacks consumed. There may be logistical and financial considerations and constraints, and these may influence the choice of method. A further problem in population studies is the need for adequate sample sizes to provide statistical robusticity and representativeness of the population of interest. Most dietary surveys adopt the simple methods of questionnaire and/or interview and translate these to nutrients and energy intakes using food composition tables. One example is the on-going National Health And Nutrition Examination Survey (NHANES) in the United States.[11] Beginning in 1966 a series of discrete surveys of the US population were undertaken until, in 1999, the survey became a continuous process assessing 5000 people each year in 15 different counties across the country. The NHANES *interview* includes demographic, socioeconomic, dietary, and health-related questions, while the *examination* component consists of medical, dental, and physiological measurements and laboratory tests.

Findings are used to determine the prevalence of major diseases and their risk factors. Information is used to assess nutritional status and its association with health promotion and disease prevention. NHANES findings are also the basis for national standards for

physical measurements such as height, weight, and blood pressure. Data from these surveys are also used in epidemiological studies and health sciences research to develop public health policy and design health programs and services.[11] While the participants are interviewed about types, quantities, and frequency of food and drink consumed in the previous 24 h, there are no direct observations of food behavior i.e. food purchased, processed or consumed. Thus the data on composition in food tables may not match those of the actual food consumed because of, for example, home-made recipes and/or the addition of unreported sauces and condiments.

There is, therefore, a compromise between ease of use, acceptability to participants, and accuracy. In some cases, simple techniques and low relative precision may be appropriate. For example. some epidemiological investigations may require individuals to be assigned only to a correct tertile (33.3% band) of intake e.g. high, medium, or low rather than to a specific intake group for essential nutrients designated by the numerical value of the intake. It is therefore crucial to decide if the nutritional methods, and their associated accuracy and precision, are appropriate for the research questions being posed. It would, for example, be inappropriate to weigh the amount of salt added to a meal if the research question simply required an answer as to whether salt was or was not added.

The UK National Diet and Nutrition Survey (NDNS) is a more recent initiative that started in 2008.[10] The NDNS "rolling program" is a continuous, cross-sectional survey designed to collect detailed, quantitative information on the food consumption, nutrient intake and nutritional status of the general population aged 1.5 years and over living in private households in the UK The survey covers a representative sample of around 1000 people per year. The NDNS provides essential evidence on the diet and nutrition of the UK population to enable Public Health England (PHE) to identify and address nutritional issues in the population and monitor progress toward public health nutrition objectives.

Both of these *national* ongoing surveys[10,11] are essential reading for students interested in nutrition and growth and provide important background to understanding national nutritional recommendations regarding food availability and dietary intakes of different demographic groups.

Determination of requirements

It is obvious that individuals vary in their dietary requirements relative to age, sex, rate of growth, levels of activity, and state of health. Therefore, we can only make statements about the probability of what an individual's requirement for a particular nutrient might be or the probability that a particular intake will be adequate or inadequate. Adequate or inadequate in this context relates to the nutrient intake below or above which it is deficient or excessive resulting in the nutritional diseases common to deficiency e.g. kwashiorkor or to excessive intake e.g. obesity.

In addition to being able to assess the adequacy of an individual's intake, dietary standards are needed to provide guidance to individuals or groups undertaking or involved in particular pursuits e.g. sports, to provide food labeling information so that we know what nutrients we are consuming, and to enable government planning for appropriate food supply to protect the population against diseases of deficiency or excess.

Specific dietary standards are not universal and differ by country and physical conditions such as season and geographical situation and agricultural policy affecting the type of staple foodstuffs and their seasonal availability.

This desire to identify an adequate nutritional intake has led to the development of a series of nutrient values based on the Gaussian distribution that describes normal i.e. usual intake (Fig. 7.1). Three descriptive statistics result from this process which correspond to the mean $\pm$ 2 standard deviations; the mean or average called the Estimated Average Requirement (EAR), the Lower Reference Nutrient Intake (LRNI), and the Reference Nutrient Intake (RNI). The EAR represents the 50th percentile or centile value, the LRNI the 2.5th centile and the RNI the 97.5th centile. Therefore this range includes 95% of values, leaving 2.5% at each end of the normal distribution. The RNI is sufficient or exceeds the intake required for most individuals and is often called the Recommended Daily Allowance (RDA). It is important to appreciate that there will be individuals who require a greater intake than the RNI because of specific needs at specific times e.g. those

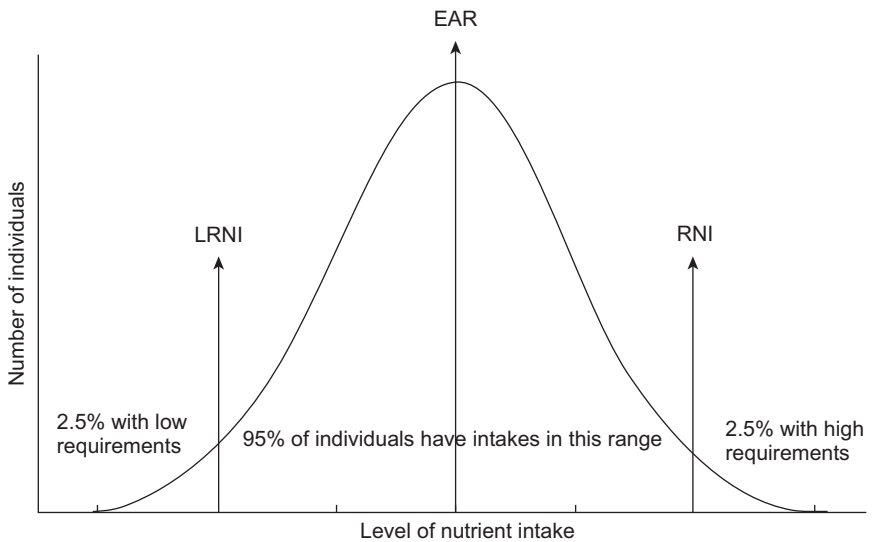

Fig. 7.1
UK dietary reference values (DRVs) superimposed on a Gaussian (normal) distribution.

involved in specific energy requiring activities such as grand tour cycling or high altitude climbing. Saris et al.[12] (1989) report that Tour de France cyclists 30 years ago (when bikes were not perhaps as light or as technically advanced as they are today) were expending five times their resting energy expenditure (about 12,500 calories) per day. Reynolds et al.[13] (1999) report that those climbing above the level of base camp on Mount Everest require 2.5−3.0 times the usual calorie intake at sea level resting energy expenditure, equivalent 5000−7500 calories per day. The problems of obtaining precise nutritional data in these circumstances are emphasized by a passage in Reynold et al.'s report (13: pp1313), "Discrepancies between actual energy expenditure and data obtained from diet records and body weight changes suggested a chronic underreporting of dietary energy intake, especially by those subjects who reached the highest altitudes. *This underreporting may be due in part to diminished cognition or to a preferential focus on survival, rather than on filling out diet records accurately.*" (my italics).

The process of growth and development is also energy expensive, particularly when the child is experiencing growth spurts, and accurate determinants of intake, and therefore assessment of requirements, are difficult to obtain because of the non-compliant nature of the child and the fact that the child is rarely involved in the processing of raw food. The researcher is thus dependent on information from a third party, usually the mother or other care giver, to provide information on the type of food, the method of processing, and the quantity consumed.

Evidence on nutrient requirements has been gained in a variety of ways. Toward the end of the nineteenth century, medical scientists investigated the types and amounts of foods associated with good health or that would lead to the reversal of signs of nutrient deficiencies. Around the turn of the twentieth century, physiologists conducted animal and human experiments on artificial and deficient diets with nutrients fed at a variety of levels to ascertain needs. These were essentially balance experiments, with allowances for growth and production. A variation has been the factorial approach, which measures all the avenues of losses from the body, e.g. urine, feces, sweat, secretions, etc., to calculate the total losses. A further approach has been to determine the level of intake associated with high or maximum levels of the nutrient in the body. This invariably produces higher estimates of requirements than the other approaches.

A problem with the balance approach is that the body can be in balance but in a state of over- or undernutrition that may be hazardous to health owing to changes or adaptations that occur to varying levels of nutrient intakes. With the outcome being a normal *pattern* of growth, two difficulties emerge; first is the identification of the range of intakes where balance is not associated with risk of over or under-nutrition; second is whether recommended intakes should be set to maintain the *status quo* or at levels that are normative and lead to balance at the lower risk range. The problem is most acute for

energy. We may calculate an allowance for children to undertake recommended amounts of Moderate to Vigorous Physical Activity (MVPA) to promote cardiorespiratory fitness and healthy body composition. However, if the children are inactive, the recommendation would result in weight gain and obesity. As usual, a decision needs be made according to the context. The Food and Agricultural Organization, World Health Organization, and United Nations University (FAO/WHO/UNU)[14] recommendations for energy intended to be applicable to individuals globally, include components for desirable but discretionary activities i.e. they are normative. On the other hand, the United Kingdom recommendations are values to maintain the *status quo*.[15]

A fourth type of value is published when there is insufficient Information to determine EAR, LRNI or RNI. In the United Kingdom, this value is called "*safe Intakes*" and is the amount that is sufficient for almost everyone in a specified group but not so large as to cause the undesirable effects of overnutrition. In the United States, when insufficient evidence exists to determine EAR, an *adequate intake* (AI) is specified. This is intended to cover the needs of most individuals in a specified group, but the percentage cannot be stated with certainty. Therefore, these are at a level comparable to RNI and RDA but have even more intrinsic uncertainty.

Finally, the maximum level that is unlikely to pose risks to health to almost all individuals in the specified group is called the *tolerable upper intake level* (UL) in the United States. This does not mean that intakes above RNI or RDA have known nutritional benefits. Also, for many nutrients, there is insufficient data on the levels at which adverse effects occur.

Energy requirements

According to FAO/WHO/UNU[14]

> *The energy requirement of an individual is the level of energy intake from food that will balance energy expenditure when the individual has a body size and composition and level of physical activity consistent with long term good health; and that will allow for the maintenance of economically necessary and socially desirable physical activity. In children and pregnant and lactating women the energy requirement includes the energy needs associated with the deposition of tissues or the secretion of milk at rates consistent with good health.*

Not every nutritionist feels comfortable with this definition, because of the problems in establishing what is a state of long-term good health and the possible subjectivity of socially desirable physical activity. However, a more immediate problem is the need to know the energy expenditure. This can be approached at a variety of levels. An estimate can be made knowing the age, sex, and weight of the child and assuming a type of lifestyle – inactive, moderately active, and so forth. At the other end of the range of approaches is measurement using stable isotopic doubly labeled water. This has the

disadvantage of being expensive and lacking information on the components of the energy expenditure. Somewhere in between is a factorial approach of recording the time and duration of activity and applying energy costs either measured or taken from the literature to these to calculate energy expenditure. There are considerable differences in the accuracy of estimates of energy expenditure from these different approaches and, hence, in the estimates of energy requirements.

Protein requirements

> *The protein requirement of an individual is defined as the lowest level of dietary protein intake that will balance losses of nitrogen in persons maintaining energy balance at modest levels of physical activity. In children and pregnant or lactating women, the protein requirement is taken to include the needs associated with the deposition of tissues or the secretion of milk at rates consistent with good health.*[14]

Protein-energy ratios

The adequacy of a protein intake is influenced by the adequacy of the energy intake. When energy intake is inadequate, there may be a net negative nitrogen balance that reduces the adequacy of the protein intake. Thus, energy and protein intakes need to be considered together. One way of doing this is the protein-energy ratio (PE ratio: protein energy/total energy). When the diet exceeds the safe PE ratio, then any protein nutrition problems will result from inadequate amounts of food rather than low protein content. Most regular diets have PE ratios between 10% and 15% i.e., protein intake is 10%−15% of total energy intake. Human breast milk has a PE ratio of about 7% and is adequate for the rapid growth in the first months of life. In the absence of other detailed information, this figure can be applied to other stages of growth. An allowance needs to be made for the efficiency of utilization of the protein, which in most cases is less than that of breast milk.

Vitamin and mineral requirements

Minimum nutrient intakes to prevent disease were common in the past, for example a recommendation for adults of 60 mg/day for vitamin C will prevent scurvy. In some countries, these minimum requirements have been increased over time, for example to 90 mg/day for vitamin C, to take into account safety factors for variation in food composition, instability resulting from unfavorable storage conditions for food, and the effects of cooking on nutrient availability. These factors, as well as the statistical considerations discussed above in relation to EARs, RDAs, and RNIs, are used to establish nutrient intake recommendations for health and performance. Further discussion of specific vitamin and mineral nutrients lies outside the scope of this chapter although some are provided in Table 7.2. Readers are recommended to consult the nutrition textbooks and internet sites listed at the end of this chapter.

Table 7.2: UIK and USA dietary intake data.

A. The United Kingdom (UK) daily Reference Nutrient Intakes (RNI) for infants and children. The UK advises one value of the RNI.			
Nutrient	**1–3 years**	**4–6 years**	**7–10 years**
Protein (g/day)	15	20	28
Iron (mg/day)	7	6	9
Zinc (mg/day)	5	6.5	7
Vitamin A (μg/d)	400	400	500
Folate (μg/d)	70	100	150
Vitamin C (mg/day)	30	30	30
Salt	2	3	5

B. The United States (USA) Recommended Dietary Allowances (RDA) for infants and children. For the energy containing nutrients protein, carbohydrates and fats the USA advises a median value and an acceptable range for the RDA.		
Nutrient	**1–3 years**	**4–8 years**
Protein (g/day)	13 (5–20)	19 (10–30)
Iron (mg/day)	7	10
Zinc (mg/day)	3	5
Vitamin A (μg/d)	300	400
Folate (μg/d)	150	200
Vitamin C (mg/day)	15	25
Salt	2.5 (1.0 as sodium)	3.1 (1.2 a sodium)

Assessment of nutritional status during childhood and adolescence

Regardless of the methods used to assess the adequacy of nutritional intake and diet quality the status of the individual, or group, in terms of growth and health are the most important outcomes.

The assessment of the nutritional status of an individual or group can be approached in several ways. We can compare the individual to some measure of an ideal body size, often termed “ideal weight”. In the majority of cases the ideal weight is actually the average weight for a given height e.g., the 50th centile weight for an individual with a height on the 50th centile. Two problem arise with this approach (1) the 50th centile height may not be associated with the 50th centile weight; (2) the 50th centile weight may in fact represent a measure of over or underweight depending on the nutritional circumstances of the source sample from which the average weight and variability were obtained. For instance, the distribution of weights in the USA during the “obesity epidemic” of the 1980s and 1990s became markedly skewed toward high weights because so many children and adults became overweight or obese. While their average weights increased their average heights did not increase by the same relative amount. Overweight and/or obesity was therefore not necessarily associated with greater heights so measures of weight-for-

height of individuals of similar heights in the 1970s and 1980s were greater in the later decade. Thus an "ideal weight" based on centile position in the 1970s would have been overweight in the 1980s and thus not "ideal".

Using average weight of a sample of children to provide a measure of good or optimal nutritional status implies that the nutritional intake that resulted in the average weight was an appropriate standard to be achieved. This is only true if the source sample is selected for the quality of their growth. The clearest example of this is the use by the WHO of the growth of a sample of exclusively breastfed infants as the standard of growth to be achieved globally.[16,17] The rationale was that as breastmilk produced by well-educated, well-nourished mothers with no habitual toxin intake, is the ideal mix of nutrients then the growth of their offspring in an unconstrained environment is *optimal*. In these circumstance that may well be true but very few samples of children experience exclusive breastfeeding and most have a short period of breastfeeding and a longer period of formula/bottle feeding.[18] However, it is these children who form the basis for growth references used nationally and internationally as a measure of normal growth i.e., the growth of children with appropriate diets.[19]

Anthropometry plays a major role in nutritional status assessment particularly in field and clinic studies of children. Growth faltering in infancy (birth to 24 months) is regarded as a clear sign and symptom of poor nutrition, and nutritionists rely heavily on anthropometry for indices of nutritional status. Not all causes of impaired growth are nutritional in origin. Most commonly, growth can be impaired by disease and infection and an associated anorexia or poor appetite. The significance of this is that the first priority may be to treat concurrent infections and eradicate their causes rather than attempt re-feeding or development projects in agriculture or subsistence food production. The provision of clean, protected water supplies and sanitation may also be an early priority (see Chapter 10).

Nutrition and growth

Assuming that a child is not suffering from a growth disorder that prevents or constrains normal growth, it is universally accepted that the size and growth rate of a child is an accurate measure of the adequacy of nutrition.[20] Should the absolute size and/or growth rate of individuals or samples of children be less than expected, inadequate nutrition is the primary cause after other known growth constraining factors e.g., hormone deficiencies, genetic disorders, psycho-social abuse, etc., have been ruled out. Differences in nutrition are thought to account for global variations in average height. The most recent (2020) pooled analysis of global trends in height over the last 35 years (1985−2019) involved 65 million participants aged 5−19 years from 2818 samples in 200 countries.[20] The authors

stated that the advantage of monitoring height and body mass index (BMI) together is that they are "… pathways from nutrition and environment during childhood and adolescence to lifelong health." The "highly variable" time trends in mean height and BMI, "indicated heterogeneous nutritional quality and life-long health advantages and risks." (p. 1512).

The relationship between nutrition and growth is both obvious and subtle; obvious because, all things being equal, poor growth relates directly to inadequate nutrition and subtle, in that the duration and severity of poor growth may be related to the lack of specific nutrients at certain critical ages, known as "critical periods", that have a long-term impact on the health and wellbeing of the child (see Chapter 3).

The adequacy of nutritional intake can therefore be simply assessed by measuring physical size and rate of growth rate and comparing them to some known value or range of values that represent normal growth. Growth charts are the instruments used for this purpose and as discussed in detail in Chapter 14, they are presented as both references and standards. Chapter 14 deals with their creation, characteristics, use, and interpretation and it will be assumed that the reader has studied that chapter and is *au fait* with the construction and use of growth charts.

Nutrition is one of several environmental influences on growth. The others include infection, poverty, poor housing, and schooling, and exposure to environmental toxicants (see Chapter 10); and it can be difficult to identify and evaluate the precise contribution of nutrition to growth or growth failure. The type, duration, and intensity of the nutritional challenge influence the nature of the response in growth, as does the ecological setting. There is thus no quantitative law-like relationship between nutrition and growth, and descriptions of the relationship tend to be rather general such as the statement that adequate nutritional intake is required to maintain normal growth.

Energy demands of growth

It is easy to move from the acceptance of adequate nutrition being required for normal growth to the idea that growth uses a significant amount of the energy from nutrient intake. This may be true for some mammals but not for humans, except for the first few months of life.

Fig. 7.2 illustrates the energy cost of growth (ECG) from birth to 18 years of age in relation to Total Energy Expenditure (TEE)[21,22] (The TEE is made up of the basal metabolic rate (BMR) and the active energy expenditure (AEE) plus the ECG which is derived from a number of empirical studies that related weight gain and fat deposition to energy intake at different ages.[21,22]

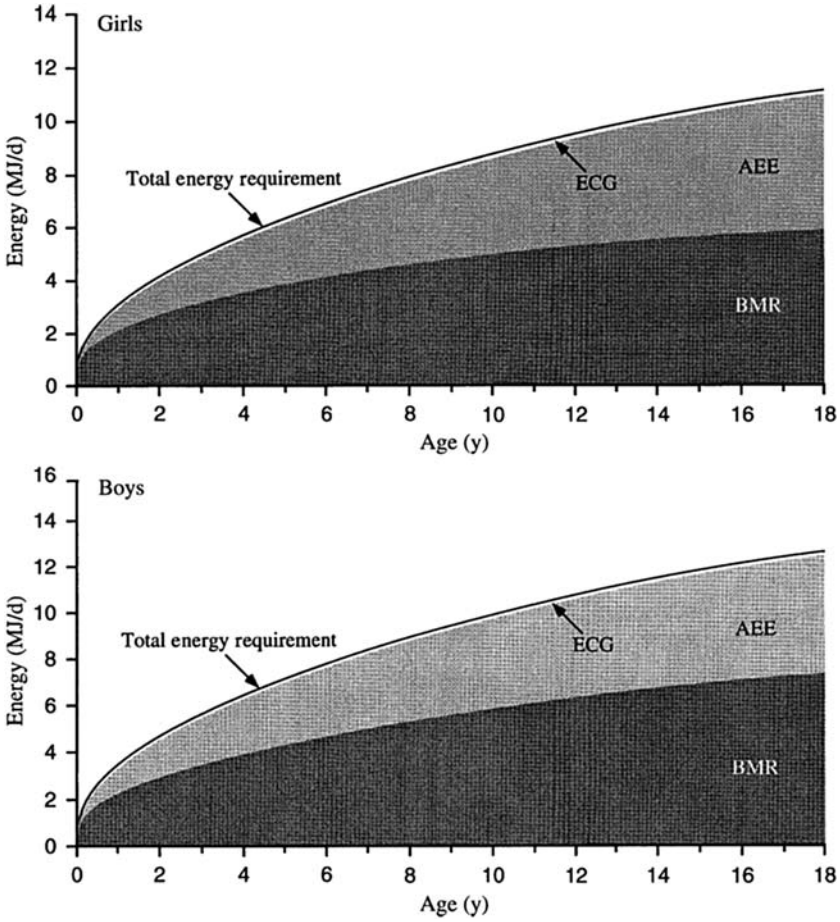

Fig. 7.2

Energy requirements of girls and boys from birth to 18 years of age partitioned into basal metabolic rate (BMR), active energy expenditure (AEE), and energy cost of growth (ECG).[21]

Table 7.3 illustrates the energy requirements of infants and children 0–24 months of age. The ECG drops rapidly during the first 6 months in both sexes from over 30% in the first month to just over 10% by the sixth month. By the end of the first year it is less than 5% of energy requirements and only 2% by 2 years of age. By contrast the energy required for physical activity increases from 20% in the first month to 30% at 2 years and BMR from 50% to 70%. So the energy cost of growth is small, but absolutely vital to maintain normal growth during this critical period.

The ECG increases at puberty and during adolescence as the reproductive system matures and the body undergoes a general growth spurt. However, the total ECG remains below 10% of the total energy intake. Despite these relatively low costs it is important to realize that growth is in the front line of responses to nutritional challenges. If energy intake falls below the needs for BMR, then either AEE or growth, or both will be curtailed.[21–23]

Table 7.3: Energy requirements of infants and children 0–24 months of age.[21]

Age (mo)	Wt (kg)	TEE (MJ/d)	BMR (MJ/d)	AEE (MJ/d)	Wt gain (g/d)	ECG (MJ/d)	ER (MJ/d)	ECG/ER (%)
Girls								
0–1	3.6	1.008	0.748	0.260	26	0.439	1.448	30.3
1–2	4.35	1.280	0.931	0.349	29	0.741	2.021	36.6
2–3	5.05	1.544	1.102	0.442	24	0.607	2.151	28.2
3–4	5.7	1.803	1.261	0.543	19	0.452	2.255	20.0
4–5	6.35	2.059	1.419	0.639	16	0.377	2.435	15.5
5–6	6.95	2.310	1.566	0.744	15	0.331	2.640	12.5
6–9	7.97	2.787	1.815	0.972	11	0.180	2.967	6.1
9–12	9.05	2.987	2.078	0.909	10	0.151	3.137	4.8
12–18	9.98	3.266	2.305	0.960	9	0.121	3.387	3.6
18–24	11.34	3.706	2.637	1.069	6	0.084	3.790	2.2
Boys								
0–1	3.8	1.038	0.946	0.091	29	0.481	1.519	31.7
1–2	4.75	1.339	1.183	0.156	35	0.841	2.180	38.6
2–3	5.6	1.628	1.394	0.233	30	0.757	2.385	31.8
3–4	6.35	1.900	1.581	0.318	21	0.506	2.406	21.0
4–5	7	2.159	1.743	0.416	17	0.364	2.523	14.4
5–6	7.55	2.402	1.880	0.522	15	0.301	2.703	11.1
6–9	8.5	2.862	2.117	0.745	13	0.192	3.054	6.3
9–12	9.7	3.201	2.415	0.786	11	0.146	3.348	4.4
12–18	10.81	3.537	2.692	0.846	7	0.096	3.633	2.6
18–24	12.08	3.948	3.008	0.940	6	0.079	4.028	2.0

AEE, activity energy expenditure; *BMR*, basal metabolic rate; *ECG*, energy cost of growth; *ER*, energy requirement; *TEE*, total energy expenditure.

Maternal and fetal nutrition and fetal growth

Maternal nutrition is, of course, intimately linked with the normalcy of fetal growth. The fetal period is critical in that infants born of low birth weight (i.e. less than 2.5 kg) are at risk of a variety of both short and long-term adverse outcomes (see Chapter 3). It has been assumed that fetal growth is relatively protected from the results of maternal under-nutrition Langley-Evans and colleagues[24] investigated the effect of maternal nutrient intakes in early and late pregnancy on fetal growth (birth weight, length, and head circumference). They concluded that, "Birth weight and infant head circumference at birth were unrelated to nutrient intakes in the first or third trimester of pregnancy … maternal nutrition in well-nourished populations does not exert a strong influence upon fetal growth." These data suggest that reported associations between low weight, thinness or greater head circumference at birth and disease in later life, are not attributable to the effects of maternal undernutrition." (p. 215). It is important to appreciate that these comments were made in the context of women in well-nourished populations who

themselves were not at risk of nutrient insufficiency. More recently Godfrey and colleagues at the University of Southampton[25] have stressed that it is unequivocal that fetal nutrition is the main driver of fetal growth however, the complex supply chain between maternal diet and fetal nutrient supply means that maternal and fetal nutrition are not the same, "… and for human pregnancies, the definition of what is optimal, in terms of maternal diet before and during pregnancy, remains unknown." (p. 1220).

Infancy and breastfeeding

The infant grows faster in the first year of life than at any subsequent period of life, and breast-feeding is recognized as the appropriate method of feeding the newborn and infant in the first months. The advantages expand beyond the provision of a feed nutritionally suited to the human infant that is hygienic and at the correct temperature. They extend to better immune competence and more protection against gastroenteritis, ear, and chest infections, eczema, and childhood diabetes. For the mother, there is a speedier reduction in size of the uterus and a lower risk of premenopausal breast cancer, ovarian cancer, and hip fracture. For a variety of reasons, some mothers choose not to breastfeed or may be unable to breastfeed. They may, for example, be unable to take time off work, and/or not be able to breastfeed at work. They may find breastfeeding painful or uncomfortable and the infant may not be taking a full feed with a consequent loss of appropriate weight gain. In these situations formula feeding (often called bottle feeding) is an alternative. While exclusive breastfeeding is recommended by the WHO for the first 6 months of life, it is debatable that infants fed formula foods in the prescribed fashion i.e. with clean water, appropriate ratio of feed to water, and clean bottles and teats, will have any short or long term adverse effects. Problems in growth arise when access to clean water and hygiene is limited and the risk of infection increases. In such situations gastrointestinal and respiratory tract infections are common resulting in poor gains in both weight and length. In acute situations this will lead to nutritional wasting (low weight for height) and in chronic situations to nutritional stunting (low height for age).

A basic assumption is that breast milk composition has evolved to meet the nutrient needs of the infant. If the amount produced is sufficient, that is, if energy needs are met, so are nutrient needs. Breast milk intake of 850 mL/day would meet the needs of infants growing along the 50th centile until 4 months old.[26] It would meet the needs of an infant in a developing country growing along the 25th percentile for 6 months. Weaning from the breast and the introduction of appropriate complimentary foods should begin at these ages.

Breast-fed babies have in the past been found to grow more slowly in infancy than formula-fed infants in some but not all studies. This meant that breast-fed children often appeared to be growing less satisfactorily than reference growth data as the older growth reference data came from groups of exclusively or mostly formula-fed infants. There is

some evidence that this difference has lessened as formula feeds have been modified toward the composition of breast milk. Fears that formula-feeding may promote the development of widespread overfeeding and obesity have not been founded. The World Health Organization (WHO) initiated a multicentre growth study in 1995 to develop a growth *standard* based on samples of exclusively breastfed infants from six countries (Brazil, Ghana, India, Norway, Oman and the USA). The construction of these growth standards is described in both Chapters 1 and 14. Briefly, the samples included infants of mothers who were well nourished, well educated, took no habitual drugs or alcohol, and provided a constraint free environment for their offspring. They exclusively breastfed their infants for 6 months according to the WHO recommendations and the growth of the infants was assessed by trained personnel every month.[16] From these data the WHO published the WHO Growth Standards for infants and children, birth to 60 months of age.[17] By calling these growth charts *standards* the WHO maintains that the patterns of growth of their sample are the way infants and children *should* grow i.e. they are *prescriptive*. Growth *references* reflect how certain groups of people *do* grow i.e. they are *descriptive* (see Chapters 1 and 14).

Certain amounts of fat, carbohydrates, protein, minerals, vitamins and water are necessary for normal growth, development, and function following weaning but how much is necessary is dependent on a variety of factors pertaining to each individual (e.g. age, sex, growth status, level of maturity, state of health and level of habitual physical activity). The real test of the adequacy of dietary intake is the appearance of the signs and symptoms of nutritional inadequacy i.e. poor growth, as a result of undernutrition or overnutrition.

Childhood and adolescence

(Chapter 3 section X.X deals in detail with nutrition and growth in childhood.)

Once weaned, children and older individuals should eat a wide variety of food, in line with the recommendations of, for example, the UK Eatwell Plate or the USA Choosemyplate. It is important to understand that reference values for nutritional intake are guidelines not recommendations. National recommendations of just how much of each nutrient is required for good health are not identical. For instance, there is currently much international debate on recommendations for vitamin D and folate (folic acid) intake. One of the biggest differences in recommendation between the UK and the USA is for calcium. The United States currently recommends an RDA of 800 mg/day for children 4–8 years old, and it rises to 1300 mg/day for 9–18 year olds. These values are based on the maximal retention of calcium in bone. In the United Kingdom the RNI for calcium is 500 mg/day for children 4–10 years old, rising to 600 or 700 mg/day for 11–18 year olds. The UK recommendations, which are substantially lower figures, are based on a factorial approach to calcium balance in the body, with allowances for gain, loss, and absorption.

Using the USA recommendation will result in more young people being classified as "calcium deficient", and this has implications for public health interventions, governmental expenditures, and general concern for parents. Both the RDA and RNI are designed to cover the needs of 97% of the population, so for most people an intake of calcium 50% lower than the RDA or RNI is likely to be sufficient for health.

Nutritional needs in adolescence may be, in absolute terms, greater than at any other time of life. The high rates of proportionate growth may only equal or be less than those of the first few months of life, but they persist for much longer. It is a time when individuals make more of their own choices in food, in some cases using them as part of a relationship struggle with parents and caregivers, but without necessarily too much nutritional knowledge. Details of adolescence nutrition are remarkably rare because the methods used to assess nutritional intake in pre-adult samples are largely based on questionnaires rather than direct observation or biomarker assessment. The questionnaires ask for food types, habitual intakes, portion sizes, and often for methods of food preparation and processing. Many adolescents have little or no idea about food preparation and provide notoriously inaccurate answers to questions relating to habitual intakes and portion sizes. They are also often inaccurate in providing information on the consumption of snacks between meals. Consequently, any knowledge of adolescent nutrition is gained from familial profiles, and parental reports. Adolescent independence, or the pursuit of it, may lead to eating disorders which, depending on its severity and duration may have transient effects on growth rates on weight, body composition and in the occurrence of amenorrhea or oligomenorrhea in girls. However, the growth of teenagers can be remarkably resilient to nutritional challenges. Diethelm[27] recently reported the nutritional intake of European adolescents and demonstrated that while the intake of most nutrients was greater than 100% of the reference value those which were less than the reference values appeared to have little effect on growth and development.

However, adolescence is characterized by rapid gains in height and weight and the extensive deposition of muscle mass and fat developed during sexually dimorphic growth and maturation which results in dramatic differences in the body composition and physiological capacity of boys and girls. The demand for nutrients increases rapidly and may exceed adult requirements. Because of the emerging sense of self with regard to body image and beliefs regarding healthy bodies, adolescence has become a prime time for the appearance of eating disorders.

Recent evidence suggests that restriction of dietary intake is commonplace to control body weight and that girls are more likely to indulge in such behaviors than boys.

Exposure to media items about body weight and dieting, parental concerns about weight gain, teasing from other children, and aspirations to share the dieting experiences of peers are all pertinent influences promoting dietary control during adolescence. An extensive

study of the development of eating disorders in Australian adolescents by Patton and colleagues in 1999 demonstrated that girls were almost 9 times more likely than boys to develop eating disorders and, if they had previously attempted to control their weight through dieting they were 16 times likely to develop eating disorders.[28]

Malnutrition

The term malnutrition cam be applied to both under and over-nutrition but it tends to be used more for the former than the latter. While the results of overnutrition have traditionally been assumed to take their toll in adulthood as non-communicable diseases (NCDs) such as cardiovascular disease or non-insulin-dependent diabetes mellitus, recent evidence demonstrates that increased risk factors for NCDs are present in from fetal life onwards (see Chapter 2). In contrast, the sequelae of undernutrition such as increased susceptibility to infectious disease, physical and mental impairment, and increased mortality mostly affect the young.

Growth retardation in developing countries is said to be most common and most marked between 6 and 12 months of age. This timing coincides with the inability of mother's breast milk to sustain infant growth and the introduction of complimentary foods. It is also a time of high growth velocities and nutritional needs, a time when the body systems are highly sensitive to stress or perturbation. If the complimentary foods given to the infant are not sufficient in energy and other nutrients, or not sanitary, then the growth of the infant will be compromised. There are long-term implications of early life stunting for health in adult life and for intergenerational effects on growth and health. These later life and intergenerational effects are discussed in detail in the Chapter 12 by Kuzawa. Kuzawa's perspective focuses on adaptations made by the fetus or infant to survive in a harsh environment.

While it is not the focus of this chapter to discuss undernutrition *per se* it is important to understand that undernutrition directly affects growth to the extent that growth parameters are used to diagnose undernutrition, The three primary diagnoses of undernutrition are underweight or thinness (low weight-for-age), stunting (low height-for-age) and wasting (low weight-for-height). It is common for undernutrition to be associated with vitamin (e.g. A, D and B12) and micro-nutrient deficiency (e.g. iron, zinc, and iodine). The severity of thinness, stunting and wasting are determined by the degree to which an individual's weight, height (length), and weight-for-height are below the average in Z-scores (Standard Deviation Scores, SDS). Mild, moderate, and severe undernutrition are defined by Z-scores of -1, -2, and -3 with each category prompting a different level and urgency of intervention to prevent long term sequelae such as permanently reduced size and cognitive ability.

UNICEF, the WHO and the World Bank work together to determine the extent of global malnutrition (see http://www.worldhunger.org/;[29] https://www.who.int/publications/i/item/jme-2020-edition;[30]). In so doing they use levels of stunting and wasting to identify undernutrition and more recently they combine this with levels of overweight. In 2019 144 million children under the age of five years − 21.3% of all such children − 47 million (6.9%) were wasted and 38 million (5.8%) were overweight.[30]

A key question is to what extent a nutritionally stunted child may catch-up in stature and weight during subsequent growth. Martorell and colleagues[31] have demonstrated that stunting prior to the age of two leaves a permanent deficit in lost height and cognitive ability. A contrary view is that the undernourished child slows down and waits for better times.[32] It seem obvious that if a child remains in the nutritional and physical environment that led to stunting, it is unlikely that this will be conducive to improvements in growth. However, catch-up between 2 and l2 years of age has been described in children from the Philippines staying in the same environment.[33] Severe stunting in the first 2 years was associated with low birth weight, which significantly reduced the likelihood of later catch-up. Positive attributes associated with catch-up were taller mothers, being the first born, and fewer siblings, which illustrates the effects of intervening non-nutritional factors.

In contrast to height deficits, weight deficits increase from childhood to adulthood in almost all populations with nutritional stunting. This may have significant and long-lasting consequences as weight-for-age and weight-for-height may be more important than height-for-age *per se* in terms of functional outcomes such as work capacity.

Improvements in the environment result in catch-up growth (see Chapter 1), but such improvements are not common and are sensitive to the timing, severity, and duration of the nutritional insult. Reports of the long-term effects of treating children with malnutrition provide evidence of catch-up, even though treatment may be for only a short period and the child returns to the same environment. Community-based supplementation studies provide better evidence of what can be achieved in the habitual environment. Any prediction as to whether catch-up growth will occur in an individual or population requires a full environmental assessment.

Relocation to better environments in the form of migration or adoption involves changes in the environment not restricted to nutrition. Studies of refugees and adoptees from South and Southeast Asia have shown accelerated growth rates, but it is not yet clear if these translate to increased adult stature. There is some evidence of accelerated puberty, which may have the effect of shortening the growth period and curtailing adult stature.

Supplementation studies

Supplementation is taken to be an addition to a diet to make up all or part of a deficiency. It can vary according to the type, amount, and duration; hence, a dose response effect

should be observed. Thus, it is a classical research design of high internal validity to demonstrate the presence of undernutrition and its effects on growth. This is also a common approach to improving maternal and child health. It might be thought that supplementing the diet of children and mothers in populations with low growth rate would inevitably result in improved growth. However, when this is attempted, the effects are usually much smaller than expected, and growth never achieves the levels of the most affluent groups in the same population or the median values in western reference data.

Several extensive supplementation studies are described in the literature. One such is the Institute of Nutrition of Central America and Panama (lNCAP) longitudinal study of the effects of chronic malnutrition on growth and behavioral development that began in 1969. It is unusual, in having a follow-up component several years after supplementation ended.[34] The study was conducted in four villages, which began with small and light mothers on low dietary intakes and with weight gains in pregnancy half those of well-nourished women; 15% of the infants died in the first year of life. Two types of supplement were provided to children up to 7 years old. Two villages selected at random were provided with *atole*, a protein-energy supplement, and the other two with *fresco*, a protein-free supplement with one-third of the energy content of *atole*. Both supplements contained minerals and vitamins. Preventative and curative medicine were provided to all villages. Supplement take-up was voluntary and so varied widely, but this allowed a dose response approach to the analyses using multiple regression, and for confounding factors to be taken into consideration.

Birth weights increased, but only by some 7 g per 10 MJ of supplement. However, low birth weight and infant mortality fell by a half in those with high supplement intakes. Energy intake was more important than protein for these improvements. In 0—3-year-old children, greater supplementation was associated with better growth in supine length and weight but not limb circumferences or skinfold thicknesses. In the highest supplementation group, these differences were 1 kg and 4 cm at 3 years old. Supplementation of 420 kJ (100 kcal) per day was associated with additional length gains of 9 mm in the first year, and 5 and 4 mm in years 2 and 3 but had no effect after 3 years of age. Children from supplemented villages continued to weigh more, be taller, and to have higher lean mass at adolescence, although differences in height were reduced compared to those at 3 years old. Other studies have been analyzed differently but show similar finding when an age-stratified approach is used. Therefore, the effects of supplementation are small and less than expected. The supplemented children did not approach the levels of height and weight seen in more affluent groups or in some other developing countries. In addition, as only some 15% of the energy of the supplement is utilized in growth processes, the fate of most of the supplement is not clear.

There are several possible explanations for this[35] related to the quality of the design and implementation of the feeding programs. Alternatively, it may be that the hypotheses and models of the processes involved have been unduly simplistic and inappropriate. The supplement may not reach the intended recipient, or it substitutes for rather than supplements the habitual diet. "Leakage" and substitution may not be failures of supplementation, as they may have benefits, albeit away from the intended recipient. The supplement may lead to increased activity, with the benefits of play and fitness and social competence, rather than growth.

Lindsay Allen,[36] in her exemplary review of nutritional influences on linear growth, concluded that there was a lack of clear, consistent evidence and that supplementation of zinc, iron, copper, iodine, vitamin A, or indeed energy or protein alone benefited linear growth in growth faltering in developed countries. In some studies, improvements were seen; in others, weight gain alone was affected; and in still others, there was no effect whatsoever. However, most of these studies have been on children older than the age at which growth faltering is most rapid. Alternatively, multiple deficiencies may be the cause of growth faltering. Except in the case of iodine, low energy diets are usually low food diets, which means low nutrient diets; that is, multiple nutrient deficiencies.

Growth retardation due to zinc deficiency was first described in the Middle East in the 1960s. Zinc deficiency was associated with high fiber, low protein diets and with parasitic infections. High-level supplementation of zinc was necessary to achieve improvements in growth presumably because the high phytate content of the high fiber diets reduced its bioavailability. Supplemental zinc has been given to low height-for-age well-nourished children in developed countries with variable effects. Linear growth is often improved but not weight gain. Often, there is no reason for these children to be zinc deficient unless they have unusually high dietary requirements for zinc. The role of zinc in the linear growth retardation of developed countries requires further work.

The most widespread dietary deficiency in the richer nations of North America and Europe is of iron. The incidence of childhood anemia has been falling at a time when iron-fortified formulas and cereals have become widespread and supplemental food programs have been introduced. Linear growth usually improves in response to iron treatment in anemic children. Iron deficiency also has non-hematological effects on behavior and cognitive performance. Non-nutritional factors, such as the social, economic, and biological environments, are important in determining the response to supplementation. In each community, different factors may operate, and there may be no circumventing the need for a full description of the ecology of the community. Our hypotheses and our models and methods of analyses may need to be refined to identify better what needs to be measured. There are, however, limits to the number of variables that can be studied, determined by the cost and quality of the data obtained. However, these studies provide

good examples of the fact that diet does not operate in isolation but in concert with other environmental challenges, such as disease, poor schooling, and general deprivation. The answer would then seem to lie in general environmental enrichment (see Chapter 16).

Overnutrition

Malnutrition in the form of overnutrition leading to overweight and/or obesity is a major nutritional problem in both developed and developing countries.[37] While overweight and obesity can arise through a positive energy balance, low levels of physical activity is also a major etiological factor. Research suggests that overweight and obesity are associated with taller childhood stature and earlier puberty.[38] However, post-natal growth rates and the timing of maturity are known to be regulated by factors operating at critical times during the fetal and infant phases of growth (see Chapter 2 and 3). The extent to which obesity in childhood persists into adulthood seems to depend on the time interval between the occurrence in childhood and adulthood. Thus, obesity in adolescence seems more persistent than obesity in childhood. However, a good deal of current work using data from cohort studies in developed and developing countries is casting new light on the relationships between the exposure of children to obesogenic environments and their subsequent growth, development and morbidity profiles.[39]

Summary

This chapter discusses the relationship between nutritional intake and growth. Initially the differences between nutrition and diet are reviewed followed by essential nutrients and the intake requirements at each of the three primary stages of growth i.e., infancy, childhood, and adolescence. The relationship between growth and nutrition is reviewed in respect to growth being used as a direct reflection of the quality of nutritional intake. Under nutrition and over nutrition are discussed relative to differences in the pattern of growth experienced by under-nourished and over-nourished children.

The adage that a certain minimal level of physical activity is required for normal growth, but it is not known what that minimum is, also true for nutritional intake except that a less or more than adequate intake has obvious, and often deleterious outcomes in terms of physical growth. The interplay between nutritional intake and the maintenance of a normal pattern of growth is often subtle involving not just quantity but also quality. It is difficult to imagine a situation in which an inadequate quantity of food is not accompanied by an inadequate intake of essential nutrients. Thus it is essential to monitor growth with an analysis of nutrient adequacy and dietary intake to assess the health and wellbeing of the child and the relationship between nutrition and growth.

Annotated Bibliography

It is important to appreciate that nutritional science is an extremely broad area of the life sciences and its fundamental reference books contain far more information than required for most students of human growth and development. Therefore, it is necessary to search for those areas that are of interest and relevance to your course of study. It is also important to appreciate that all life sciences are dynamic subjects constantly changing in response to changes in human biological and social development. Most text or reference books take two or more years to be written and published therefore they will never be current but always lag a little behind the most up-to-date information. Regularly checking reputable and trusted websites and the latest scientific publications through keyword searches of PubMed and Medline is an important habit for students to acquire.

Acknowledgment

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Nutrition Textbooks

The British Nutrition Foundation publishes a series of excellent reference books on Nutritional Science some of which contain useful sections on child nutrition from birth to young adulthood. Their website is extremely helpful: https://www.nutrition.org.uk/test.

However, the following reference books contain useful and mostly up to date material.

Langley-Evans S. *Nutrition, Health and Disease: A Lifespan Approach*. 2nd ed. Chichester: Wiley Blackwell; 2015. Available in softback, hardback and as an E-book. (University library purchase results in free access for students).

Gibney MJ, Margetts BM, Kearney JM, Arab L. *Public Health Nutrition*. 1st ed. Oxford: Blackwell; 2004, 2017 (2nd ed) Available in softback, hardback and as an E-book. (University library purchase results in free access for students).

Gibney MJ, Lanham-New SA, Cassidy A, Vorster HH, eds. *Introduction to Human Nutrition*. 2nd ed. Wiley-Blackwell; 2009.

Internet resources

Many internet resources are given in the main text of this chapter. A few additional sites are: https://www.nutrition.org.uk/.

The International Obesity Task Force with a section on childhood obesity and links to other obesity sites is at http://www.iotf.org.

WHO breastfeeding: https://www.who.int/en/news-room/fact-sheets/detail/infant-and-young-child-feeding.

Breastfeeding stats UK : https://pubmed.ncbi.nlm.nih.gov/29888866/.

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Food Standards Agency. FSA Nutrient and Food Based Guidelines for UK Institutions. http://www.food.gov.uk/multimedia/pdfs/nutguideuk.pdf.

WHO websites: http://www.who.int/childgrowth/mgrs/en/.

http://www.who.int/childgrowth/standards/en/.

UK National Diet and Nutrition Survey: https://www.gov.uk/government/collections/national-diet-and-nutrition-survey).

USA National Health and Nutrition Survey: https://www.cdc.gov/nchs/nhanes/about_nhanes.htm.

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CHAPTER 8

The genetic epidemiology of growth and development

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Introduction

This chapter provides an overview of the genetic epidemiology of normal human growth and development. It serves as an introduction to how human growth researchers can most efficiently study the genetics of human growth and development with the methods and approaches currently available.

Nearly three-quarters of a century ago Neel and Schull[1] proposed that the epidemiological approach can be extended to the study of non-diseased states, and argued that, "… genetic concepts must be an integral part of the armamentarium of the modern epidemiologist." (p. 302). The "epidemiological genetics" that Neel and Schull[1] had envisioned has become known today as "genetic epidemiology." Following from this perspective, the genetic epidemiology of growth and development may be considered as the study of the genetic underpinnings of the size, conformation, and maturity status of individuals over the course of childhood. This includes characterizing the magnitude of genetic influences on growth and development phenotypes, examining how those genetic influences operate over time, identifying and localizing genes and specific genetic polymorphisms in those genes that contribute to variation in growth and development, and elucidating how genetic and environmental factors interact during growth and development. The advances made over the past several decades in both molecular and statistical genetics have led to vast amounts of biological data, high-powered computer resources, and highly sophisticated statistical and bioinformatics methods of analysis. These resources combine to facilitate gaining a better understanding of the roles of genes, environmental factors and their interactions in the complex biological processes that comprise growth and development.

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This chapter is divided into three additional sections that follow below. Section II provides an introduction to basic statistical genetic terminology. Section III discusses different study designs used to examine genetic influences on growth-related traits and Section IV provides a brief overview of published findings from various seminal and recent studies of the genetics of growth and development. Throughout the chapter, important terms or concepts are underlined the first time they are mentioned. Those that are not defined in the text of the chapter are briefly defined in the Glossary.

Statistical genetic terms and concepts

Statistical genetics refers to a variety of methods for analyzing phenotypic variation among related individuals. These methods include those tailored for the study of both discrete and continuous traits. Most growth and development phenotypes exhibit a continuous distribution over a delimited range, and because the growth and development status of a child can usually be measured in some way, most growth and development phenotypes are quantitative traits. Growth and development phenotypes are also often referred to as being complex traits, meaning that genes at a few and perhaps several loci contribute to the variation observed in the trait, as do environmental factors, likely through interaction with those genes. The field of quantitative genetics deals with the analysis of complex traits. As with any specialized field of study, it contains a number of specific terms and concepts. This section provides a brief discussion of those quantitative genetic terms and concepts most important for understanding the genetic epidemiology of normal growth and development. Thorough discussion of quantitative genetic methods can be found in books listed in "Further Reading" at the end of this chapter.

Relatedness of individuals

To start with, because related individuals are not independent, but share some of their genes by virtue of sharing common ancestry, it is necessary to consider their degree of relatedness in assessing the extent of their resemblance for a trait. The coefficient of kinship between two individuals is the probability that an allele taken at random from the two alleles at a locus in one individual is identical to an allele taken at random from the two alleles at the same locus in another individual. The coefficient of kinship between first degree relatives is 0.25, meaning that, for example, between a pair of full siblings there is a 25% chance that they each have at a locus the very same allele that they each inherited from a common ancestor. Most of what we know about the genetic control of growth and development comes from family-based studies in which the correlations between relatives and between unrelated individuals for a trait such as stature or weight are calculated. The basic premise underlying these investigations is straightforward - if the variation in a trait is largely under genetic control, then related individuals will be more similar for the trait

than will unrelated individuals (i.e., the intra-family variance of the trait is low compared to the inter-family variance). Conversely, if the variation in a trait is only partly determined by genes, then related individuals may only resemble each other a little bit more so than do unrelated individuals (i.e., the intra-family variance of the trait is a little smaller than the inter-family variance).

Heritability

From examination of correlations among different relative pairings, heritability estimates can be calculated. The concept of heritability (h^2) is central to understanding the nature of genetic control for any trait in a population. The h^2 of a trait is a measure of the degree of genetic control of a particular trait, ranging from 0 (no genetic control) to 100% (complete genetic control). Heritabilities are population level estimates, specific to a particular population in a given environment. This is always an important consideration when comparing h^2 estimates across populations.

According to classical quantitative genetics theory (e.g., see texts Falconer and Mackay 1996, Lynch and Walsh 1998)[2,3] the observed phenotypic variation (σ^2_P) in a trait can be expressed as the sum of both genetic (σ^2_G) and random environmental effects (σ^2_E). This is written as

$$\sigma^2_p = \sigma^2_G + \sigma^2_E \tag{1}$$

In its simplest form, this model provides a starting point for understanding the quantitative genetics of complex traits. For example, σ^2_P can be decomposed further into components representing the variance due to the additive effects of genes at several loci (σ^2_A), dominance effects (σ^2_D), and even epistasis (σ^2_I). While σ^2_E can be decomposed into the variance due to specific measured environmental factors ($\sigma^2_{E\ \text{factor \#1}}$) and that due to random, unmeasured environmental factors ($\sigma^2_{E\ \text{random}}$). Broad sense heritability refers to the proportion of the phenotypic variance attributable to all sources of genetic variance, and is written as

$$h^2 = \sigma^2_G / \sigma^2_P \tag{2}$$

Narrow sense heritability refers to the proportion of the phenotypic variance attributable only to the additive genetic variance, and is written as

$$h^2 = \sigma^2_A / \sigma^2_P \tag{3}$$

Generally, the narrow sense heritability is the most useful in characterizing the genetic effects of continuous traits such as stature or weight. Inheritance of these quantitative traits is likely to be influenced by a number of genes exerting mostly small to moderate effects. For that reason, quantitative traits are often referred to as being polygenic traits. However,

not all genes influencing a trait likely make the same contribution to the phenotypic variance of the trait. Also, since it is typically very difficult (e.g., because of sample size constraints) to identify genes explaining only a small proportion of the phenotypic variance of a trait (e.g., 1% or less), it is perhaps more practical to refer to most quantitative traits as being oligogenic traits, meaning that it is likely that a few genes with pronounced and identifiable effects of varying degrees are together responsible for most of the genetic contribution to the phenotypic variance of a trait. In most instances h^2 estimates refer to narrow sense heritabilities. The variance components approach to decomposing the phenotypic variation exhibited in a quantitative trait briefly described here is an elegant and powerful method for evaluating the different sources of variation contributing to the overall variance of a complex trait.

Genetic and environmental correlations

Quantitative genetics is much more than calculating h^2 estimates. Since it is well established that measures of growth and development have substantial and significant heritable components, intellectual focus turns to better understanding the nature of the genetic regulation of growth and development. For example, significant phenotypic correlations often exist between different measures of growth and development. These phenotypic correlations may be due to pleiotropy, the joint effects of a gene or genes on different traits, or to shared environmental factors. In most cases, significant phenotypic correlations between two traits are due to some degree of both pleiotropy and shared environmental effects.

Just as the phenotypic variance of one trait can be decomposed into genetic and environmental variance components, so too can the phenotypic correlation between two traits can be decomposed into genetic and environmental covariance components. Thus, the phenotypic correlation between two traits is a function of the h^2 of each trait and the genetic and environmental correlations between them. This is written as

$$\rho_P = \sqrt{h_1^2}\,\sqrt{h_2^2}\,\rho_G + \sqrt{(1-h_1^2)\sqrt{(1-h_2^2)}\,\rho_E} \tag{4}$$

where ρ_p is the phenotypic correlation, ρ_G is the genetic correlation, ρ_E is the environmental correlation, h_1^2 is the heritability of trait 1 and h_2^2 is the heritability of trait 2.

As with phenotypic correlations, additive genetic and random environmental correlations range from -1.0 to 1.0. A genetic correlation of 1.0, for example, indicates complete positive pleiotropy between two traits. That is, there are genes that affect in the same manner both of the traits being examined. A genetic correlation significantly less than one

indicates incomplete pleiotropy, meaning that the two traits are influenced to some extent by the same set of genes, but that other genes also are influencing the value of one or the other of the two traits. A genetic correlation of zero between two traits indicates that the two traits have different genes controlling them. Finally, a negative genetic correlation indicates that the same set of genes operates in an opposite manner on the two traits. Similarly, the random environmental correlation is a measure of the direction and strength of the correlated response of two traits to non-genetic factors. If specific non-genetic factors have been identified and measured that influence the covariance of the two traits, however, then the environmental correlation can be decomposed into non-random and random components.

Multivariate quantitative genetic analyses, in which the heritabilities of two (or more) traits are estimated along with the genetic and environmental covariances between them, are powerful tools for investigating the nature of relationships between different aspects or measures of growth and development.

Applications of genetic and environmental correlations to longitudinal data

Another topic of particular interest in the field of growth and development is the nature of the genetic control of a trait over time. For these types of analyses, it is necessary to have serial measurements of the trait or traits of interest. Serial measurements of traits separated by time are normally correlated to some degree, with higher phenotypic correlations often found over short intervals and lower phenotypic correlations found over longer intervals. Canalization is a familiar term to auxologists, referring to the tendency of a trait to follow a certain course or trajectory over time. The more highly canalized a trait, the higher the phenotypic correlations between repeated measurements. From a genetic perspective, traits that are highly canalized, and that are relatively insensitive to changes in environmental conditions, are likely to have relatively high heritabilities. The same genes, however, may or may not be influencing the trait to the same extent over the entire course of growth and development.

To test hypotheses concerning the genetic control of growth at different ages, the same approach discussed above for the examination of two traits at one point in time is taken. In its simplest form, however, the "two traits" can also be the same trait measured at two points in time. The genetic and environmental correlations between repeated measures of the trait at different ages are then calculated. This approach allows for disentangling shared genetic effects from shared environmental effects on a trait measured over the course of childhood.

The strength of a genetic correlation for a single trait with repeated measures is indicative of the degree of consistency or uniformity in the genetic control of the trait over time. For example, if a genetic correlation of 1.0 is observed between stature measured at age 8

years and measured again at age 18, then it can be inferred that the genes influencing stature during the middle of childhood are the same as those that influence height in early adulthood. If a genetic correlation is obtained that is significantly lower than 1.0, however, then there is evidence that a different suite of genes control stature at ages 8 and 18 years. Similarly, the environmental correlation is a measure of the consistency or uniformity of the response of the trait to non-genetic factors over time. We will return to a discussion of gene-by-age interaction after first discussing the theory underlying gene-by-environment and gene-by-sex interactions.

Gene-by-environment interaction

Understanding how genes interact with aspects of the physical and internal biological environments is essential for better understanding the genetic architecture of complex traits. In studies where relatives live in different environments, gene-by-environment (GxE) interactions can be examined using extensions of variance components methods for studying quantitative trait variation.

GxE interaction is likely an important influence on the variation observed among children in their growth and development, particularly in populations with high prevalence of environmental factors known to negatively impact growth and development. The key to GxE interaction, however, is that not all children respond the same to such environmental factors, and a portion of that differential response may be due to genetic variation among individuals.

The simplest approach to modeling GxE interaction is to make the genetic variance in a trait a function of a dichotomous environmental variable. Examples of this could be the presence or absence of a particular disease in a child, high or low protein intake, etc. Fig. 8.1 shows a simple hypothetical depiction of the response of three genes at a locus to two different environments. In the presence of GxE interaction, the relationship between trait levels and specific genes will vary as a function of the environment. In this case, trait levels in Environment 1 are substantially less variable compared to trait levels in Environment 2. For genes AA and AB, trait levels remain stable or decrease from Environment 1 to Environment 2. For gene BB, trait levels increase from Environment 1 to 2. This example demonstrates how gene expression may vary under different environmental conditions.

In GxE analyses of the response of a quantitative trait, the variance components method is expanded to include environment-specific additive genetic variances that are then estimated. For example, a large number of related children might be measured for a trait (e.g., stature) at a specific age, and also tested for the presence of a particular infection at that age. If the additive genetic variances of the measured trait are not significantly different between infected and non-infected children, then that would be an indication that

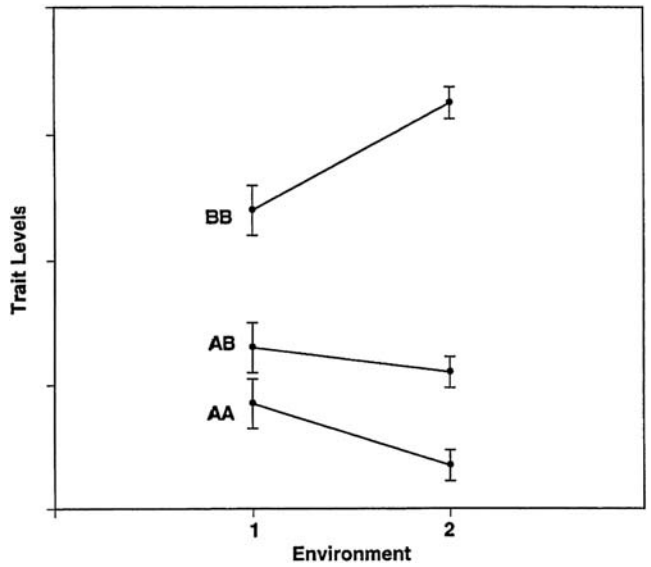

Fig. 8.1
Hypothetical depiction of genotype-by-environment interaction with the response of three genotypes at a locus to two different environments.

there is no GxE interaction between that trait and that infection at that age. If, on the other hand, the additive genetic variances of the measured trait are significantly different between infected and non-infected children, then that would indicate a genetic basis to the differential response of the growth status of children to infection at that age. GxE interaction is also tested by examining the genetic correlation between the trait measured in different environments. A genetic correlation significantly different from 1.0 is another indication of GxE interaction. In the example here, a genetic correlation significantly less than 1.0 would indicate that the GxE interaction is due to an incompletely correlated genetic response of the trait in infected and non-infected children.

Gene-by-sex interaction

Sexual dimorphism in the growth and development of children is well known, but the genetic basis of this sexual dimorphism is poorly understood. The approach for studying GxE interaction using related individuals living in different environments described above can be used to study gene-by-sex (GxS) interactions. The rationale here being that the hormonal environments of males and females differ considerably, and the expression of autosomal genes controlling a quantitative trait may be influenced by the sex-environment encountered.

In analyses of GxS interaction, the variance components method is again expanded. Additional parameters are estimated, the most important being sex-specific variance

components and the genetic correlation between the sexes for the trait. GxS interaction is indicated by significantly different additive genetic variances for males and females and/or a genetic correlation between the sexes significantly less than 1.0.

GxS interaction analyses can be used to examine the genetic basis to the sexual dimorphism in measures of growth and development. The aim of GxS interaction analyses is to determine if the sexual dimorphism evidenced in a trait during childhood age is itself a heritable trait. In some families, for example, male and female children might not be very different in a measure of growth or development at a particular age, while in other families there might be significant differences between male and female relatives in that measure of growth or development at that age.

Gene-by-age interaction

The nature of genetic influences on measures of growth and development may change over the course of childhood. As initially discussed earlier, the genetic correlation between a trait measured at two points in time can provide insight into the genetic control of a trait over time. If extensive longitudinal data from related children are available, gene-by-age (GxA) interactions can be more rigorously examined. Like GxS interactions, GxA interactions are a type of GxE interaction. In this case, the "environment" is the age of the child at the time of the measurement of a trait. In these analyses, the additive genetic variance of a trait is modeled as a function of age. From these age-specific additive genetic variances, age-specific heritabilities of the trait can be determined. Also estimated are the additive genetic and environmental correlations between the trait measured across two or more time points.

GxA interaction is indicated by an additive genetic variance of a trait changing over a span of ages. This suggests that the genetic expression of a trait is dependent upon the age of the child. GxA interaction also is indicated by a change in the genetic correlation between a trait measured over time. For example, a genetic correlation between time points of a serially-measured trait that decreases significantly from 1.0 over a span of ages indicates GxA interaction. And, if sufficient serial data are available, the function or shape of a genetic correlation curve can provide further insights into dynamic genetically-mediated biological processes underlying such GxA interactions.

Identifying genes influencing growth and development

Once it has been determined that a trait has a significant heritability, interest quickly turns to locating and identifying the actual genes that influence variation in the trait. Advances in molecular and statistical genetic methods make it possible to search for genes and specific genetic polymorphisms influencing complex traits. Unlike monogenic traits that

are influenced by a single gene with large effects, most complex traits are largely (but not exclusively) influenced by genes at a number of loci whose individual effects can be of small to moderate size. While understanding of monogenic growth disorders has significantly increased over the last several decades, understanding the genetics of normal variation in quantitative measures of growth and development has continued to be a daunting task. Technological advances in molecular biology, however, including relatively inexpensive high-throughput genotyping of upwards of millions of single nucleotide polymorphisms (SNPs) and increasingly lower cost exome and whole-genome sequencing, along with attendant methodological advances in statistical genetics, have made it possible to identify genes exerting small or moderate effects and to even identify rare polymorphisms influencing a trait in only some populations or pedigrees. There are two basic strategies to follow in the search for genes involved in the regulation of growth and development: population-based association studies or family-based quantitative trait linkage studies.

Population-based association studies

The first approach is the candidate gene association approach. Here, genes suspected to be physiologically involved in the trait are examined. For example, a sample of unrelated individuals is selected and genotyped for a specific polymorphism in or near the candidate gene. Simple statistical tests are then used to evaluate associations between marker genotype status and the value of a trait. Carriers of a particular allele, for example, may have a mean value for the trait that is significantly different than the mean value of the trait in those who do not have a copy of that allele. Population-based association studies have obvious appeal - they are computationally straightforward compared to the analysis of marker genotype and quantitative trait data from family members.

There is a significant problem with population-based association studies, however, that has become evident as greater knowledge has been gained regarding linkage disequilibrium. Two loci are in equilibrium when alleles at the two loci are randomly associated with each other. If the relationship between the loci is not random, then linkage disequilibrium is present. Unfortunately, linkage disequilibrium can occur for a number of reasons including new mutations, genetic drift, and in the presence of selection. The main problem with association studies, however, is that disequilibrium cannot be predicted. Two loci may be very close to each other and yet be in equilibrium. Conversely, two loci may be relatively far apart from each other and yet be in disequilibrium. There is no sure way to know that the marker that has been typed is in disequilibrium with the trait that has been measured. If it is known *a priori*, however, that the typed marker is in fact a functional polymorphism (that is, there is a measurable difference among marker genotypes in gene expression; e.g., one genotype results in much lower levels of a particular protein compared to the other genotypes), then association studies become a more viable strategy to pursue.

Genome-wide association studies

In recent years, genome-wide association (GWA) studies of complex traits have proliferated. GWA analysis is an extension of the candidate gene association approach, and is made possible by relatively low cost genotyping of now typically from 500,000 to 1,000,000 single nucleotide polymorphisms (SNPs) in each subject in a study sample. SNPs are bi-allelic genetic markers that are coded either "0" or "1", and are most often separated by only fairly small intervals across the entire genome. Associations between genotypes and phenotypes are evaluated over every marker. Of course, given the large number of markers, these analyses are computationally intensive and stringent strategies to control for multiple testing must be followed.

GWA study designs typically take one of two forms. One is the case-control approach where individuals with a certain disease or condition are compared to unaffected individuals with regard to genotype status at every genotyped SNP across the genome. SNPs that are significantly more prevalent in either cases or controls are identified for follow-up to assess possible causative or protective roles of nearby functional polymorphisms. A second GWA study design focuses on quantitative traits where different genotypes at a single locus are examined for differences in trait levels. Associations are denoted when individuals with certain SNP genotypes have consistently and significantly higher or lower trait values than individuals with the other SNP genotypes.

There are several strengths to the GWA approach. First, the high density of SNP markers helps to better localize association signals. GWA signals can be typically reduced to approximately a 500 kb interval, compared to a much broader interval obtained from quantitative trait linkage discussed below. Another strength, alluded to above, is that data can be obtained from unrelated individuals potentially making data collection more efficient. Indeed, numerous GWA studies have been based on already existing epidemiological study samples. Potential problems with population stratification can be ameliorated by using principal component-based (or ancestral marker-based) adjustments obtained from the SNP marker set. Replication of findings is critically important for GWA studies, however, given the large number of comparisons made across the genome in a single study. Such replication of significant findings provides confirmation of the role that at least common polymorphisms play in contributing to phenotypic variation. All GWA studies should include plans for some form of replication in independent samples.

Despite the popularity of GWA studies over the last two decades, important criticisms of the approach have emerged in recent years. To date, GWA studies have collectively had somewhat limited success, despite numerous published studies and several large meta-analyses of various complex traits that have sometimes included samples sizes of

over 100,000 subjects. In most cases, reported associations have accounted only for a very small proportion of the overall heritability of the traits examined. Some researchers speculate that the reason for this is that GWA studies are only useful for identifying common disease variants. Unfortunately, it now appears that many common disease or quantitative risk factor variants only explain a relatively small proportion of the total phenotypic variance in the disease or trait examined. The population-based association approach is therefore less likely to be able to identify rare disease variants that are most likely to have larger effect sizes.

Additionally, significant associations can be due to heterogeneity in the population sampled. This occurs when population subgroups differ systematically in both allele frequencies and levels of the quantitative trait of interest. Even among seemingly fairly homogeneous families (e.g., similar ethnic background) there can be significant differences in specific allele frequencies; and all families carry unique "private" polymorphisms, some of which may impact a trait in some families but not in others.

Family-based samples have recently proved useful for GWA studies. In fact, family-based designs are optimal for identifying rare genes of moderate to large effect sizes as noted above due to the fact that unique "private" polymorphisms are often enriched in families. GWA studies from family-based samples can be several times more powerful compared with population-based studies of an equal number of participants, depending upon the complexity of the family structure. Large extended pedigrees can be five to seven times more powerful for gene discovery studies given that there is a substantial expected increase in genotypic dosage variance induced by Mendelian transmission in pedigree-based samples.

Quantitative trait linkage analysis

Another approach for discovering genes influencing traits of interest to auxologists is quantitative trait linkage mapping. Linkage studies require a good deal of planning prior to their initiation in order to obtain maximal statistical power to detect genes of modest to moderate effect. The premise behind linkage analysis is that if two loci are physically located close to each other, then alleles at these loci will be more likely to be inherited together. In this case, the loci are said to be linked. As the distance between loci increases, the probability that alleles at these loci will cross-over or recombine during meiosis increases. Through investigation of the frequency of recombination events among genetic markers one can identify chromosomal regions harboring genes that influence variation observed in a trait. Once a region has been identified, molecular mapping techniques such as high-density SNP typing or sequencing can be used to better delineate chromosomal regions of interest and to identify functional polymorphisms.

Over the last two decades there have been many advances in quantitative trait linkage analysis as applied to complex traits. Over that time, allele-sharing methods have gained prominence for the analysis of quantitative traits. The key premise behind allele-sharing methods is the concept of identity by descent (IBD). In comparisons between relatives, two alleles that are structurally identical are said to be identical by state (IBS), alleles that are structurally identical and inherited from a common ancestor (e.g., two siblings getting the same allele from their mother) are further classified as IBD. A pair of relatives can share 0, 1, or 2 alleles IBD at any given marker locus. The likelihood of their sharing 0, 1, or 2 alleles IBD is contingent upon their coefficient of kinship. Linkage between a quantitative trait locus (QTL) and a marker exists in chromosomal regions when pairs of relatives who are more phenotypically similar share more alleles at a marker locus than pairs of relatives who are less phenotypically similar.

The power to detect and localize QTLs is a function of several factors, the most important being the strength of the genetic effect. Traits that are highly heritable will tend to have a higher probability of being mapped compared to those with low to modest heritability, but this is not always the case. Also, as in any statistical analysis, sample size is of importance, but in linkage studies other aspects of the study sample are also important, most especially the family structure of the study sample. Having many families is good, but having fewer more complex extended pedigrees, preferably with several generations represented, will yield increased statistical power because of the greater number and variety of relationships between relatives.

Linkage analysis has several strengths and some weaknesses. One strength of linkage analysis is the ability to identify rare genetic variants in family-based samples. Because genes segregate in families, the ability to identify rare genes of moderate effect is possible. Identification of rare variants may help to explain what has been termed the "missing heritability" observed from population-based GWA studies of common traits (i.e., the portion of the heritability not explained by the common variants).[4] Rare variants are likely to have larger effect sizes and could contribute to the unexplained heritability. Further, some researchers suggest that these rare variants are likely to have obvious functional consequences.[4,5] A benefit of pedigree-based studies for the identification of rare variation is that rarer variants, if present, will be present at a much higher frequency than in the general population. Thus, pedigree-based studies inherently have greater power to detect the effects of such rare variants. However, traditional linkage-based studies have limited resolution (due to typically having fewer genetic markers typed, although this is somewhat ameliorated with SNP-based linkage analysis vs. earlier STR-based linkage analysis; see also below) and are only able to localize QTL to approximately 10−15 Mb of sequence, a much broader region compared with GWA studies.

Quantitative trait linkage and association

In recent years there has been an effort to combine both linkage and association approaches. This approach effectively utilizes the strength of both genetic paradigms. Combined linkage and association analysis can only be accomplished with family-based data, however. As a first step, a family-based approach to association analysis (e.g. measured genotype) can be implemented to test for associations assuming additive genetic effects on each available SNP in the panel.[6,7] Since data from family members cannot be treated as independent observations, family based methods such as variance-component analysis are able to use a polygenic component to absorb any non-independence among individuals by incorporating a residual heritability parameter. In this context, quantitative trait linkage provides an additional, independent source of information that, when used in conjunction with GWA, can augment power to detect loci influencing growth-related traits. SNPs used for linkage can be selected from among the typed SNP panel to maximize heterozygosity and minimize LD among the selected markers. Approximately 10,000 SNPs are required for adequate genomic coverage in SNP-based linkage analysis. A joint test of linkage and association can performed by comparing the likelihood of a model in which both the SNP-specific association parameter and the linkage variance component are estimated to the likelihood of a model in which both are constrained to be zero. The power of this test depends on the underlying trait model and on how many functional variants there are within a gene or region; however, under certain circumstances combined linkage and association can be more powerful than association alone. In the coming years, the field of genetics will continue to move toward use of more advanced technology and recent studies have focused on whole genome and whole exome sequencing as the cost of sequencing has become more affordable for large population studies.

Mendelian Randomization

Mendelian randomization (MR) is an interesting statistical technique that has gained popularity in recent years.[8–14] It is a genetic tool that can be used to make assertions regarding whether or not causal relationships can be identified from statistical associations between a risk factor variable and an outcome measure. In this approach, known genetic variants for the risk factor (SNPs) are screened against the outcome variable. If a significant association is observed between the genetic variant (referred to as the instrument variable or IV) and the outcome variable, there is evidence for a causal relationship between the risk factor and the outcome. In practice there are three core assumptions to this approach. These assumptions are relevance, independence, and exclusion restriction.[14] They are detailed below, respectively, (1) the IV (i.e., the genetic variant) must be associated with the risk factor; (2) the IV must NOT be associated with any measured confounding variable (a confounder is variable that is associated with both

the risk factor and the outcome variable); and (3) the IV influences the outcome only through the risk factor of interest. There are additional analytical methods that can account for varying degrees of violations to the standard assumptions.

One recent study, conducted by Warrington et al.,[15] used Mendelian randomization to examine the influences of maternal and fetal genetic effects on birthweight and their influence on future cardio-metabolic disease risk in adulthood. In this example, birthweight was considered the risk factor for future cardio-metabolic risk (the outcome) in later life. Using a complex series of analysis, the researchers observed that the commonly observed association between lower birth weight and higher adult blood pressure was likely attributable to genetic effects, and not to intrauterine programming. Given the widespread availability of genetic marker data collected in large human populations, we can expect the use of Mendelian randomization to expand in the coming years, as it provides an additional level of information over and above traditional studies of phenotypic association.

Study designs

Various family-based study designs can be used to examine the genetics of complex traits. Each study design has certain advantages and disadvantages. This section describes some of the major types of study designs used by genetic epidemiologists to study complex quantitative traits and their potential application to growth studies.

Twin studies

Over the years, studies of twins have been useful in establishing the familial aggregation of many complex traits. In its basic form, the twin model compares phenotypic differences between two classes of twins, monozygotic (MZ) and dizygotic (DZ). MZ twins share 100% of their genetic make-up, while DZ twins share on average only half of their genetic make-up (i.e., on the genetic level they are the same as any other pair of full sibs). Because of this, phenotypic differences observed between MZ twins are assumed to be the result of environmental factors only, while phenotypic differences between DZ twins are considered to be due to differences in both genes and environmental exposure. Thus, by calculating phenotypic correlations in groups of MZ and DZ twins and comparing them, assumptions can be made about the degree of genetic control of different traits.

One important assumption in the classical twin study design is that both MZ and DZ twin pairs are equally likely to share a common environment. This assumption may not necessarily be valid, however, because MZ twins are often more likely to share common activities, foods and other aspects of the environment to a greater extent than DZ twins.

Because there is no fully satisfactory way to separate shared genetic and environmental effects, studies of twins often yield inflated h^2 estimates.

The twin study design is especially problematic if the focus of the study is a growth-related outcome. Twin births are physiologically different from singleton births due to competition over maternal resources during pregnancy. Fetal growth rates among twins may therefore be considerably discordant, and the postnatal growth of twins is often different from that of siblings from singleton births (e.g., early catch-up growth in twins).

Nuclear families

Another commonly used study design is that of nuclear families. In this study design, correlations between the various classes of first-degree relatives in a nuclear family are estimated. These include parent-offspring and sibling-sibling correlations. Heritabilities can be estimated from these different familial correlations. Heritability estimates calculated from nuclear family data, however, are subject to inflation due to the effects of shared environmental factors such as diet and lifestyle among family members living in a single residence. Given this, heritabilities are often adjusted by taking into account the degree of spousal correlation in the family. It is assumed that any correlation found between spouses is the result of shared environmental factors. Such spousal correlations may depend upon the length of time that the couple has been married. But, such spousal correlations may also be the result of assortative mating.

There are practical considerations to be taken into account in studies of nuclear family members apart from those just mentioned. For example, it is sometimes difficult to obtain information about certain life events because they are often separated in time by a generation - it may take 20−30 years of waiting to collect growth measures of the children of parents who were measured when they were children. Also, generational differences in growth may be due to secular trends. This may effectively reduce the heritability of certain traits by diminishing the degree of phenotypic correlation observed. These two problems can be eliminated by examining only sibling correlations, but the problem of shared environment remains.

Extended pedigrees

The study design that offers considerable promise for elucidating the genetic architecture of complex traits is the extended family approach. This approach involves collecting information from all available family members and estimating phenotypic correlations between all relatives of varying degrees of relationship. By sampling members outside of the immediate nuclear family, many of the problems encountered with immediate shared environmental effects in other study designs are minimized because family members come

from a number of different households. This results in more accurate and reliable h^2 estimates. In addition, by sampling family members in different households (who thereby live in potentially different environmental circumstances) there is the opportunity to investigate GxE interactions. With regard to the study of growth and development, within large extended pedigrees there will be several related children of approximately the same age. This will enable analyses to proceed very quickly after the initiation of data collection.

There are a few practical drawbacks to this approach, however. The single most important consideration is that the methods involved in calculating statistical genetic parameters can be computationally intensive. This, however, is much less of an obstacle as computer technologies continue to progress. Indeed, advances in computer technology over the last three decades have made the statistical genetic analyses of data from large pedigrees tractable. Also, collecting data from large numbers of related individuals of varying ages and who may live some distance from each other requires a great deal of planning, effort, and continued research funding.

Studies of the genetics of growth and development

The preceding sections introduced several basic terms and concepts regarding genetic epidemiological approaches to growth and development. This section provides a brief overview of the numerous studies of genetic influences on growth and development that have been conducted over the last century. The review presented here provides a sampling of this literature, focusing on studies of height, birth weight, and measures of development including menarche, peak height velocity, and skeletal development.

Population differences in growth and development

There is considerable variation across populations in growth in height, weight, and other body dimensions, as well as in the tempo and timing of maturation.[16] For example, mean adult height varies from approximately 150 cm for males in the shortest populations on earth (e.g. Mbuti people of central Africa) to 180 cm for males in Northern European populations. These long standing observations of racial or ethnic differences in growth and development rendered support for the notion that genetic factors are likely involved. The degree to which genetic factors influence growth and development cannot be addressed, however, by the simple comparison of measures of growth and development traits across populations. The populations compared often are exposed to vastly different environments, and the shortest and smallest populations also tend to have the poorest economic status, while the tallest populations tend to be from industrialized nations. Between-population differences may be due to differences in both genetic and environmental factors, whose relative importance is often confounded. For example, evidence of secular trends in stature

and pubertal maturation,[16] and the degree of similarity for stature in high socioeconomic status groups from various parts of the world (e.g., Martorell 1988),[17] argue that a significant part of inter-population variation in growth and development is due primarily to environmental factors.

Family studies of growth and development

Population comparisons provide only indirect evidence of a connection between genetic factors and phenotypic variation in growth and development. Only family studies within populations can clearly define the relationships between genes and growth, because it is with these designs that environmental and genetic sources of variation can be explicitly modeled.

As an initial overview of genetic influences on growth and development, Table 8.1 summarizes published familial correlations and/or the heritability estimates for birth weight, height, weight, and other anthropometrics, as well as age at menarche in females, from a large selection of family studies from diverse populations. Table 8.1 does not contain an exhaustive listing of all published findings, but provides a starting point; the studies listed in Table 8.1 were published in widely circulated journals and represent the range of findings typically reported in the literature.

Several general comments can be made regarding these investigations. First, most studies have been based on first-degree familial correlations. That is, they are based on either nuclear family or twin pair designs. And, as discussed above, there are important concerns when studying only first degree relatives - particularly when studying growth and development. These concerns include secular trends that may reduce correlations between parents and offspring, and the shared environments of siblings, especially twins, that may inflate correlations between them. Second, specific shared environmental sources of variation such as diet and disease status usually have not been incorporated into the analyses. Not accounting for the variance in a trait attributable to such environmental factors can lead to overestimation of the h^2 of the trait. Third, the majority of studies have focused solely on height at a given point in time (mostly adult height). A smaller number of studies have examined other anthropometrics. Fourth, the majority of studies are based on cross-sectional data. Only a few studies have longitudinal growth and development data from related individuals that permit examination of genetic influences on patterns of change in height, weight, and other measures over time. And fifth, almost all of the studies have focused solely on heritability estimation. There are very few multivariate quantitative genetic analyses of measures of growth and development, or analyses of gene-by-environment, sex, or age interactions.

Table 8.2 highlights recently published results from GWA or linkage analyses of birth weight, height, body mass, and age at menarche. This continues to be an expanding area

Table 8.1: Heritability estimates of anthropometrics during childhood and adolescence.

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
Birth weight							
	Penrose[18]	UK	Cross-sectional, nuclear			Fetal genetic factors: 18% Maternal genetic factors: 20% Environmental factors: 62%	Birth
	Morton[19]	Japan	Cross-sectional, nuclear/twins		rtwins = 0.56 rsibs = 0.52 rhalfsibs-mo = 0.58 rhalfsibs-fa = 0.10		Birth
	Nance et al.[20]	US	Cross-sectional, nuclear/twins	Offspring of 385 twin pairs	rsibs = 0.48 rhalfsibs-mo = 0.31 rhalfsibs-fa = −0.03		Birth
	Clausson, Lichtenstein, and Cnattinigius[21]	Sweden	Cross-sectional, twins	868 MZ 1141 DZ		$h^2 = 0.25–0.40$	Birth
	Magnus et al.[22]	Norway	Cross-sectional, trios (Fa, Mo, first born)	67,795 trios	rfa-mo = 0.02 rfa-off = 0.129 rfa-son = 0.126 rfa-dau = 0.133 rmo-off = 0.226 rmo-son = 0.222 rmo-dau = 0.231	$h^2 = 0.25$	Birth
	Van Dommlen et al.[23]	Netherlands	Longitudinal, twins	4649 twin pairs		$h^2 = 0.14$ $h^2 = 0.24$	Birth, females Birth, males
	Arya et al.[24]	US (Mexican americans)	Cross-sectional, nuclear/extended	840 subjects		$h^2 = 0.72$	Birth
	Grunnet et al.[25]	Denmark	Cross-sectional, twins	138 MZ 214 DZ	rMz = 0.75 rDz = 0.56	$h^2 = 0.38$	Birth
	Choh et al.[26]	US	Longitudinal, nuclear/extended	917 subjects		$h^2 = 0.67$	Birth

Height/Recumbent length							
	Vandenberg and Falkner[27]	US	Longitudinal, twins Stature curve parameters)	29 MZ 31 DZ	Concordance between MZ and DZ twins: MZ = DZ initial value (birth) MZ < DZ (velocity) MZ < DZ (acceleration)		Birth-6 years
	Welon and Bielicki[28]	Warsaw, Poland	Longitudinal, nuclear	496 parent-child pairs	rparent-son = 0.36 rparent-son = 0.43 rparent-da = 0.54 rparent-da = 0.59		Age: 8 years, male Age: 18 years, male Age: 8 years, female Age: 18 years, female
	Garn, Bailey, and Cole[29]	US	Cross-sectional, (adopted/ biological siblings)	6726 biological 504 adoptive parent-offspring pairs	radopted sibs = 0.29 radoptive - biological sibs = 0.35		Birth − 18 years
	Malina, Mueller, and Holman[30]	US white and black	Cross-sectional, nuclear	422 black families 384 white families		$h^2 = 0.49$ (white) $h^2 = 0.37$ (black)	Age: 6−12 years
	Mueller[31]	Colombia, Africa, Peru, new Guinea, Japan	Cross-sectional, nuclear		rpc = 0.29 (average)		
	Mueller[31]	US, UK, West Europe, East Europe	Cross-sectional, nuclear		rpc = 0.37 (average)		
	Wilson[32]	US	Longitudinal, twins	159 MZ 195 DZ	rMZ = 0.58 rMZ = 0.94 rDZ = 0.69 rDZ = 0.61		Birth Age: 4 years Birth Age: 8 years

Continued

Table 8.1: Heritability estimates of anthropometrics during childhood and adolescence.—cont'd

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
	Fischbein[33]	Sweden	Longitudinal, twins	94 MZ 233 DZ	rMZ = 0.90 rDZ = 0.60–0.70		Age: 10–16 years
	Mueller and Titcomb[34]	Colombia	Cross-sectional, nuclear	403 families	rmo-child = 0.28 rfa-child = 0.27	$h^2 = 0.49$ (males) $h^2 = 0.47$ (females)	Age: 7–12 years
	Susanne[35]	Belgium	Cross-sectional, nuclear	125 families	rpc = 0.51	$h^2 = 0.82$	Age: 17–35 years
	Roberts, Billewicz, and McGregor[36]	West Africa	Cross-sectional, nuclear, full and half siblings	276 sibships		Fa-child: $h^2 = 0.61$ Mo-child: $h^2 = 0.85$ Midparent-child: $h^2 = 0.65$ Full siblings: $h^2 = 0.81$ Paternal half-siblings: $h^2 = 0.56$	
	Fischbein and Nordqvist[37]	Sweden	Longitudinal, twins	94 MZ 133 DZ	Average growth profile similarity within twin pair: rMZ = 0.85 rDZ = 0.54		Age: 10–16 years (growth curve concordance)
	Kaur and Singh[38]	India	Cross-sectional, nuclear	82 families	rpc = 0.48	$h^2 = 0.92$	Age: 18–59 years
	Solomon, Thompson, and Rissanen[39]	Finland	Cross-sectional, nuclear	2869 subjects		$h^2 = 0.58$	Age: < 55 years
	Devi and Reddi[40]	India	Cross-sectional, nuclear	436 families	rpc = 0.34 rsibs = 0.33	$h^2 = 0.65$	Age: 6–13 years
	Sharma et al.[41]	India	Cross-sectional, nuclear/twins	610 subjects	rsibs = 0.30 rDZ = 0.59 rMZ = 0.98		Age: 3–26 years
	Byard, Guo, and Roche[41]	US	Longitudinal, nuclear (height growth curve parameters)	228 families	Age at TO: rpc = 0.17, rsibs = 0.32 TOV: rpc = 0.26,		Age: 2–18 years

					rsibs = 0.35 Age at PHV: rpc = 0.22, rsibs = 0.35 PHV: rpc = ns, rsibs = 0.32		
	Towne et al.[42]	US	Longitudinal, nuclear/extended (height curve parameters)	569 subjects		Recumbent length at birth: $h^2 = 0.83$ Velocity 0 −2 years: $h^2 = 0.67$ Acceleration change 0 −2 years: $h^2 = 0.78$	Age: 0−2 years
	Hauspie et al.[43]	Poland	Longitudinal, twins (stature curve parameters)	44 MZ 42 DZ		Age at TO: $h^2 = 0.49$ Age at PHV: $h^2 = 0.74$ PHV: $h^2 = 0.76$	Age: 8.5 years −adulthood
	Beunen et al.[44]	Belgium	Longitudinal, twins	99 twin pairs		Age at TO: $h^2 = 0.93$ TOV: $h^2 = 0.90$ age at PHV: $h^2 = 0.92$	Age: 10−18 years
	Price et al.[45]	US (African American)	Cross-sectional, extended families	1185 families	rpo = 0.26 rsib = 0.27		Age: 18−92 years
	Price et al.[45]	US (Caucasian)	Cross-sectional, extended families	1185 families	rpo = 0.37 rsib = 0.37		Age: 18−92 years
	Silventoinen et al.[46]	Finland	Longitudinal, twins	3466 MZ 7450 DZ		$h^2 = 0.66$−0.82	Birth cohorts 1928- earlier through birth cohort 1947−57
	Luke et al.[47]	Jamaicans	Cross-sectional, nuclear, extended	623 subjects		$h^2 = 0.74$ $h^2 = 0.44$ $h^2 = 0.84$	Mean age: 39.5 years Mean age: 38.8 years Mean age: 37.5 years

Continued

Table 8.1: Heritability estimates of anthropometrics during childhood and adolescence.—cont'd

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
	Silventoinen et al.[48]	Finland	Longitudinal, twins	4873 twin pairs		$h^2 = 0.78–0.87$	Birth cohort 1938–49
	Silventoinen et al.[48]	Finland	Longitudinal, twins	2374 twin pairs		$h^2 = 0.67–0.82$	Birth cohort 1975–79
	Arya et al.[49]	India	Cross-sectional, nuclear	1918 subjects (342 families)		$h^2 = 0.36$	Age: 6–72 years
	Brown et al.[50]	US	Longitudinal, nuclear	2885 subjects		$h^2 = 0.88$ $h^2 = 0.88$ $h^2 = 0.88$	Age > 40 years Age > 55 years Age > 70 years
	Silventoinen et al.[51]	Multiple European nationalities	Longitudinal, Twins	30,111 twin pairs		$h^2 = 0.84–0.93$	Age: 20–40 years
	Li et al.[52]	Chinese	Nuclear	1169 subjects (385 families)		$h^2 = 0.65$	Mean age: Fa = 62.3 years, Mo = 59 years, Da = 31 years
	Schousboe et al.[53]	Denmark	Longitudinal, twins	299 male twin pairs 325 female twin pairs		$h^2 = 0.69$ $h^2 = 0.81$	Age: 18–67 years Age: 18–67 years
	Van Dommlen et al.[23]	Netherlands	Longitudinal, twins	4649 twin pairs		$h^2 = 0.10$ $h^2 = 0.44$ $h^2 = 0.52$ $h^2 = 0.15$ $h^2 = 0.74$ $h^2 = 0.58$	Birth females Age: 1 year females Age: 2 years females Birth males Age: 1 year males Age: 2 years males
	Malkin et al.[54]	Chuvashes (Russia)	Cross-sectional, nuclear	743 subjects		$h^2 = 0.87$	Age: 18–89 years males age: 17–90 years females

	MacGregor et al.[55]	Australian	Longitudinal, twins	618 MZ females 239 MZ males 338 DZ females 143 DZ males 334 DZ OS	rMZ = 0.92 rMZ = 0.92 rDZ = 0.44 rDZ = 0.39 rDZ = 0.42	$h^2 = 0.911$	Age: 32–44 years
	Saunders and Gulliford[56]	UK	Longitudinal, extended families	22297 subjects		$h^2 = 0.49$	Standardized for age
	Bayoumi et al.[57]	Arab	Cross-sectional, consanguineous	1277 subjects		$h^2 = 0.68$	Age: 16–80 years
	Czerwinski et al.[58]	US	Longitudinal, nuclear/extended	403 subjects		$h^2 = 0.98$	Mean age: 38.5 years
	Dubois et al.[59]	Canada (Quebec)	Longitudinal, twins	85 MZ, 92 DZ		$h^2 = 0.445$ $h^2 = 0.223$ $h^2 = 0.241$ $h^2 = 0.54$	Birth Age: 5 month males Age: 5 month females Age: 60 month
	Pan et al.[60]	Hutterites	Longitudinal, extended, multiple lines of descent	806 subjects		$h^2 = 0.90$	Age: 6–89 years
	Reis et al.[61]	Brazil	Cross-sectional, twins	5 MZ 9 DZ		$h^2 = 0.95$	Mean age: 13 years
	Silventoinen et al.[62]	Netherlands	Longitudinal, twins	7753 pairs (at age 3)		$h^2 = 0.71–0.79$ $h^2 = 0.58–0.71$	Age: 3–12 years males Age: 3–12 years females
	Silventoinen et al.[63]	Sweden	Longitudinal, twins	99 MZ 76 DZ male twin pairs		0.97	Age: 17.5–20 years
	Silventoinen et al.[64]	Sweden	Multiple, twins/siblings	1582 MZ 1864 DZ 154970 full brother pairs		0.81	Age: 16–25 years
	Axenovich et al.[65]	Dutch	Cross-sectional, extended pedigrees	2940 subjects		0.86	Mean age: 48.26 years
	Jowett[66]	Mauritius	Cross-sectional, extended pedigrees	400 subjects		$h^2 = 0.84$	Mean age: 50 years
	Mathais et al.[67]	Chennai (South India)	Cross-sectional, extended families	498 subjects from 26 pedigrees		$h^2 = 0.72$	Mean age: 42.65 years

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Table 8.1: Heritability estimates of anthropometrics during childhood and adolescence.—cont'd

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
	Poveda et al.[68]	Belgian	Cross-sectional, nuclear	460 subjects		0.84	Age: 17—72 years
	Choh et al.[26]	US	Longitudinal, nuclear/extended	917 subjects		$h^2 = 0.95—0.96$ $h^2 = 0.74—0.95$	Age: 30 —36 month Age: 0 —24 month
Weight							
	Garn et al.[29]	US	Cross-sectional, (adopted/ biological siblings)	6726 biological, 504 adoptive parent-offspring pairs	radopted sibs = 0.18 rbiological sibs = 0.27		Birth-18 years
	Wilson[32]	US	Longitudinal, twins	159 MZ 195 DZ	rMZ = 0.61 rMZ = 0.86 rDZ = 0.68 rDZ = 0.55		Birth Age: 4 years Birth Age: 8 years
	Fischbein[33]	Sweden	Longitudinal, twins	94 MZ 233 DZ	rMZ = 0.80—0.90 rDZ-males = 0.60—0.70 rDZ-females = 0.70—0.20		Age: 10—16 years
	Mueller and Titcomb[34]	Colombia	Cross-sectional, nuclear	403 families	rmo-child = 0.36 rfa-child = 0.31	$h^2 = 0.16$ (males) $h^2 = 0.21$ (females)	Age: 7—12 years
	Susanne[35]	Belgium	Cross-sectional nuclear	125 families	rpc = 0.34	$h^2 = 0.64$	Age: 17—35 years
	Fischbein and Nordqvist[37]	Sweden	Longitudinal, twins	94 MZ 133 DZ	Average growth profile similarity within twin pair: rMZ = 0.79 rDZ = 0.22 (females) rDZ = 0.53 (males)		Age: 10—16 years Growth curve concordance
	Kaur and Singh[38]	India	Cross-sectional nuclear	82 families	rpc = 0.34	$h^2 = 0.39$	Age: 18—59 years

	Arya et al.[49]	India	Cross-sectional, nuclear	1918 subjects (342 families)		$h^2 = 0.314$	Age: 6–72 years
	Van Dommelen et al.[23]	Netherlands	Longitudinal, twins	4649 twin pairs		$h^2 = 0.64$ $h^2 = 0.58$ $h^2 = 0.55$ $h^2 = 0.59$	Age: 1 years females Age: 2 years females Age: 1 years males Age: 2 years males
	Estourgie-van Burk et al.[69]	Netherlands	Cross-sectional, nuclear/twins	478 MZ males 517 DZ males 561 MZ females 478 DZ females 962 DZ opposite sex		$h^2 = 0.59$ $h^2 = 0.78$	Age: 5 years males Age: 5 years females
	Dubois et al.[59]	Canada (Quebec)	Longitudinal, twins	85 MZ 92 DZ		$h^2 = 0.399$ $h^2 = 0.871$ $h^2 = 0.9$ $h^2 = 0.877$	Birth Age: 5 month males Age: 5 month females Age: 60 month
	Silventoinen et al.[64]	Sweden	Multiple, twins, siblings	1582 MZ pairs, 1864 DZ pairs, 154970 full brother pairs		$h^2 = 0.64$	Age: 16–25 years
	Choh et al.[26]	US	Longitudinal, nuclear/extended	917 subjects		$h^2 = 0.74$–0.85	Age: 1–36 month
Biacromial breadth							
	Mueller and Titcomb[34]	Colombia	Cross-sectional, nuclear	403 families	rmo-child = 0.33 rfa-child = 0.32	$h^2 = 0.63$ (males) $h^2 = 0.40$ (females)	Age: 7–12 years
	Susanne[35]	Belgium	Cross-sectional, nuclear	125 families	rpc = 0.33	$h^2 = 0.58$	Age: 17–35 years
	Kaur and Singh[38]	India	Cross-sectional, nuclear	82 families	rpc = 0.38	$h^2 = 0.75$	Age: 18–59 years

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Table 8.1: Heritability estimates of anthropometrics during childhood and adolescence.—cont'd

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
	Devi and Reddi[40]	India	Cross-sectional, nuclear	436 families	rpc = 0.30 rsibs = 0.37	$h^2 = 0.49$	Age: 6–13 years
	Sharma et al.[41]	India	Cross-sectional nuclear/twins	610 subjects	rsibs = 0.32 rDZ = 0.56 rMZ = 0.95		Age: 3–26 years
	Arya et al.[49]	India	Cross-sectional, nuclear	1918 subjects (342 families)		$h^2 = 0.44$	Age: 6–72 years
	Salces et al.[70]	India	Mixed-longitudinal, nuclear	238 brothers 214 sisters (134 families)		$h^2 = 0.30–1.0$	Age: 4–19 years
Biiliac breadth							
	Susanne[35]	Belgium	Cross-sectional, nuclear	125 families	rpc = 0.49	$h^2 = 0.73$	Age: 17–35 years
	Devi and Reddi[40]	India	Cross-sectional, nuclear	436 families	rpc = 0.18 rsibs = 0.18	$h^2 = 0.34$	Age: 6–13 years
	Ikoma et al.[71]	Japan	Cross-sectional, nuclear	3632 subjects	rsibs = 0.30 rpc = 0.27	$h^2 = 0.54–0.55$	Age: > 14 years
	Salces et al.[70]	India	Mixed-longitudinal, nuclear	238 brothers 214 sisters (134 families)		$h^2 = 0.47–1.0$	Age: 4–19 years
Upper arm circumference							
	Mueller and Titcomb[34]	Colombia	Cross-sectional, nuclear	403 families	rmo-child = 0.37 rfa-child = 0.32	$h^2 = 0.20$ (males) $h^2 = 0.34$ (females)	Age: 7–12 years
	Susanne[35]	Belgium	Cross-sectional, nuclear	125 families	rpc = 0.30	$h^2 = 0.50$	Age: 17–35 years
	Kaur and Singh[38]	India	Cross-sectional, nuclear	82 families	rpc = 0.23	$h^2 = 0.24$	Age: 18–59 years
	Devi and Reddi[40]	India	Cross-sectional, nuclear	44 MZ 436 families	rpc = 0.26 rsibs = 0.24	$h^2 = 0.46$	Age: 6–13 years
	Sharma et al.[41]	India	Cross-sectional, nuclear/twins	610 subjects	rsib = 0.26 rDZ = 0.52 rMZ = 0.95		Age: 3–26 years

	Arya et al.[49]	India	Cross-sectional, nuclear	1918 subjects (342 families)		$h^2 = 0.301$	Age: 6–72 years
	Poveda et al.[68]	Belgian	Cross-sectional, nuclear	460 subjects		$h^2 = 0.57$	Age: 17–72 years
Age at menarche							
	Damon et al.[72]	US	Retrospective, nuclear	78 mo-da pairs	rmo-da = 0.24		
	Orley[73]	Hungary	Retrospective, nuclear	550 mo-da pairs	rmo-da = 0.25		
	Kaur and Singh[38]	India	Retrospective, nuclear	72 mo-da pairs	rmo-da = 0.39		
	Brooks-Gunn and Warren[74]	US	Retrospective, nuclear (daughters)	307 mo-da pairs	rmo-da = 0.26 (non-dancers) rmo-da = 0.32 (ballet dancers)		Age: 14–17 years
	Meyer et al.[75]	Australia	Retrospective, twins	1178 MZ	rMZ = 0.71 rDZ = 0.22	$h^2 = 0.17$ (additive effects) $d^2 = 0.54$ (dominance effects)	
	Malina, Ryan, and Bonci[76]	US	Retrospective, nuclear (University athletes)	109 mo-da pairs 77 sib pairs	rmo-da = 0.25 rsib = 0.44		
	Loesch et al.[77]	Poland	Longitudinal, twins (examined genetic correlations among maturity traits)	95 MZ female 97 DZ female		h^2 (raw) = 0.95 $h^2 = 0.44$ (unique genetic effects) $h^2 = 0.53$ (shared genetic effects with skeletal maturity)	Age: 0–18 years
	Kirk et al.[78]	Australian	Longitudinal, twins	1001 pairs, 708 subjects	rMZ = 0.51 rDZ = 0.17	$h^2 = 0.5$	Mean age: 13 years
	Sharma et al.[79]	India	Cross-sectional, twins	60 female twin pairs (30 MZ, 30 DZ)	rMZ = 0.93 rDZ = 0.55	$h^2 = 0.78$	Mean age: 17.5 years

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Table 8.1: Heritability estimates of anthropometrics during childhood and adolescence.—cont'd

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
	Towne et al.[80]	US	Longitudinal, nuclear/extended	371 subjects		$h^2 = 0.46$	Age: 9–16 years
	Pan et al.[60]	Hutterites	Longitudinal, extended, multiple lines of descent	806 subjects		$h^2 = 0.46$	
				BMI			
	Magnussen and Rassmussen[81]	Sweden	Cross-sectional, extended/nuclear	196,743 sons, 19,972 fathers	Full bro = 0.36 Mat half bro = 0.21 pat half bro = 0.11 father-son = 0.28		Age: 18–19 year
	Silventoinen et al.[62]	Netherlands	Longitudinal, twins	7753 pairs (at age 3)		$h^2 = 0.60–0.78$ $h^2 = 0.57–0.82$	Age: 3–12 years males Age: 3–12 years females
	Haworth et al.[82]	UK	Longitudinal, twins/nuclear	3582 twin pairs (at age 3)		$h^2 = 0.48$ $h^2 = 0.65$ $h^2 = 0.82$ $h^2 = 0.78$	Age: 4 years Age: 7 years Age: 10 years Age: 11 years
	Silventoinen et al.[64]	Sweden	Multiple, twins/siblings	1582 MZ pairs, 1864 DZ pairs, 154970 full brother pairs		$h^2 = 0.59$	Age: 16–25 years
	Wardle et al.[83]	UK	Longitudinal, twins	5092 twin pairs		$h^2 = 0.77$	Age: 8–11 years
	Lajunen et al.[84]	Finland	Longitudinal, twins	2413 twin pairs		$h^2 = 0.69$ $h^2 = 0.58$ $h^2 = 0.66$ $h^2 = 0.58$ $h^2 = 0.83$ $h^2 = 0.74$	Age: 11–12 years males Age: 11–12 years females Age: 14 years males Age: 14 years females

							Age: 17 years males Age: 17 years females
	Martin et al.[85]	US	Longitudinal, nuclear	821 subjects		$h^2 = 0.70$	Mean age: 12.6 years
	Salsberry and Reagan[70]	US	Longitudinal, mother-offspring	5453 subjects 4994 subjects		$h^2 = 0.29$ $h^2 = 0.20$ $h^2 = 0.61$ $h^2 = 0.56$	Age: 6–8 years males Age: 6–8 years females Age: 12–14 years males Age: 12–14 years females
	Choh et al.[86]	US	Longitudinal, nuclear/extended	1176 subjects		$h^2 = 0.43–0.78$	Age: 0–36 month Age 4, 7, 11, 15,19 years
Growth pattern parameters							
	Beunen et al.[87]	Belgium	Longitudinal, twins	99 twin pairs		Adolescent stature growth curve parameters: $h^2 = 0.89–0.96$	Age: 10–18 years
	Van Dommlen et al.[23]	Netherlands	Longitudinal, twins	4649 twin pairs		Stature at different ages: $h^2 = 0.12–0.44$ $h^2 = 0.33–0.74$	Birth-2.5 years females Birth-2.5 years males
	Czerwinski et al.[58]	US	Longitudinal, nuclear/extended	403 subjects		Adolescent stature growth curve parameters: Age at PHV: $h^2 = 0.72$ PHV: $h^2 = 0.65$ Height at PHV: $h^2 = 0.98$	Age: 2–18 years
	Silventoinen et al.[63]	Sweden	Longitudinal, twins	99 MZ males 76 DZ males	rMZ = 0.92 rDZ = 0.41	$h^2 = 0.93$	Age: 17.5–20 years

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Table 8.1: Heritability estimates of anthropometrics during childhood and adolescence.—cont'd

Trait	Reference	Population	Design and family structure	Sample size	Familial correlations	Heritability or genetic variance estimate	Age range
	Towne et al.[88]	US	Longitudinal, nuclear/extended	579 subjects		Midchildhood growth spurt: $h^2 = 0.37$	Age: 2—18 years
	Choh et al.[26]	US	Longitudinal, nuclear/extended	917 subjects		Instantaneous weight, height velocity $h^2 = 0.49$ —0.78, 057 —0.99	Age: 0—36 month

Da, daughter; *DZ*, dizygotic twins; *Fa*, father; *Mo*, mother; *MZ*, monozygotic twins; *PHV*, peak height velocity (pubertal height velocity maximum); r_{pc}, parent-child correlation; r_{sib}, sibling correlation; *TO*, "Takeoff" (height velocity minimum); *TOV*, "takeoff" velocity (pre-pubertal height velocity minimum).

Table 8.2: Recent large-scale genetic association studies of growth and development traits.

Trait	Reference	Population/s	Study design	N (discovery and replication)	Trait age range	Number of significant loci identified	% Of variance explained by identified loci
Age at menarche							
	Liu et al.[89]	EU, Chinese	GWA	3480	~ 9–17 years	1	–
	Perry et al.[90]	EU	GWA	17,510	9–17 years	2	–
	Elks et al.[91]	EU	GWA	102,533	9–17 years	42	3.6–6.1%
	Sulem et al.[92]	EU, Icelandic	GWA	20,954	7–19 years	1	–
	Shi et al.[93]	Chinese/ Korean	GWA	16,395	N/A	19	–
	Day et al.[94]	EU, Iceland	GWA, MR	329,345	N/A	389	7.2–7.4%
Birth weight							
	Freathy et al.[95]	EU	GWA	38,214	Birth	2	0.3–0.1%
	Kilpelainen et al.[96]	EU	Association study of 12 obesity-susceptibility loci	28,219	Birth	2	–
	Horikoshi et al.[97]	EU	GWA	153,781	Birth	60	
	Warrington et al.[15]	EU	GWA, MR	321,223	Birth	190	~7.0%
BMI							
	Den Hoed et al.[98]	EU	Association study of 16 obesity susceptibility loci	13,071	9–16 years	9	1%
	Kang et al.[99]	African	GWA	1931	18–74 years	0	–
	Graff et al.[100]	EU	GWA	29,880	16–25 years	7	–
	Felix et al.[101]	EU	GWA	35 668	2–10 years	15	2%
	Vogelezang et al.[102]		GWA	61,111	2–10 years	25	3.6%

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Table 8.2: Recent large-scale genetic association studies of growth and development traits.—cont'd

Trait	Reference	Population/s	Study design	N (discovery and replication)	Trait age range	Number of significant loci identified	% Of variance explained by identified loci
Height							
	Soranzo et al.[103]	EU	GWA	19,798	16—99 years	17	<0.20%
	Kang et al.[99]	African	GWA	1931	18—74 years	14	0.20%
	Lango et al.[104]	EU	GWA	183,727	Adults	180	10%
	Lanktree et al.[105]	6 ethnicities	Association study of 2000 cardiovascular disease susceptibility loci	114,223	21—80 years	64	—
	Wood et al.[106]	EU	GWA	253,288	Adults	697	21—29%
	He et al.[107]	East Asia	GWA	93,926	Adults	98	8.9%
Growth pattern parameters							
	Sovio et al.[108]	EU	Association study of 43 height-related loci	3538	0—31 years	24	—
	Couto Alves et al.[109]	EU	Meta analyses/ GWA	6051—7215 depending on trait	0—24 mo.	3 for age-AR, 4 for BMI-AR, 1 for PWV	—

age-AR, age at infant adiposity rebound; *BMI*, body mass index; *BMI-AR*, BMI at infant adiposity rebound; *EU*, European; *GWA*, genome-wide association; *MR*, Mendelian Randomization; *PHV*, peak height velocity; *PWV*, peak weight velocity; *SNP*, single-nucleotide polymorphism.

of auxological genetics research as primary research interest has shifted to identifying specific genes and genetic variants that influence such measures. Again, Table 8.2 does not contain an exhaustive listing of all published findings, but provides a starting point for entry into the literature.

Birth weight

The genetics of prenatal growth has largely been approached by examining the heritability of birth weight. Initially, genetic influences on birth weight were deduced from the known effects of quantitative changes in chromosomes. For example, supernumerary autosomes (trisomy 21, 18, and 13) and abnormal numbers of X chromosomes (as in Turner syndrome) all result in growth retardation. Formal quantitative genetic analyses of birth weight find somewhat lower heritability estimates than for body weight and length in postnatal life, which are both highly heritable (see below). Assessment of genetic influences on birth weight is complicated, however, by the fact that prenatal growth (at least as measured by birth weight) is influenced by both the genetic makeup of the fetus and the maternal intrauterine environment, and there is no fully satisfactory way to partition these two sources of variation. Therefore, not surprisingly, estimates of the influences of fetal genes, maternal genes, non-genetic maternal factors, and random environmental effects on fetal growth vary considerably across studies. The role of fetal genes varies from 0 to 50%, maternal factors from 27 to 50%, and random environmental factors from 8 to 43% in the variation in birth weight.[110]

For example, a classic study by Penrose[18] attempted to partition the variance in birth weight among fetal genes, maternal genes, non-genetic maternal factors, and random environmental effects. He concluded that fetal genes accounted for approximately 18% of the phenotypic variance, while "maternal factors" (a combination of both genetic and uterine environment) explained approximately 40% of the phenotypic variance. The importance of the uterine environment in the control of prenatal growth is also demonstrated by the changes in twin correlations from birth onwards (e.g., Wilson[32]). Intra-pair differences in the birth weight of MZ twins are often significant at birth (tending to be larger than differences between DZ twins) because MZ twins compete for placental resources. Differences in weight between MZ twin decreases over time. By 3 years of age, the MZ twin correlation is about 0.80−90 and the DZ twin correlation is about 0.40−0.50.

A problem with the use of birth weight as a measure of prenatal growth is that it represents growth status at a variety of maturational ages depending on gestational age. Most studies of the genetics of birth weight have often not controlled adequately for gestational age. This flaw has likely led to under-estimates of genetic influences. Indeed, using a variance components method for pedigree data, and modeling a gestational age covariate effect, we have found a high heritability of birth weight in the Fels Longitudinal Study population ($h^2 = 0.81$).[111] Continued work along these lines will help to identify

specific factors influencing fetal growth and development. However, progress depends on measurement strategies that better capture the process of fetal development (e.g., serial ultrasound biometry).

Height

Data from nearly 4000 individuals in 1100 nuclear families in England analyzed by Pearson and Lee[112] provide perhaps the earliest evidence for the inheritance of height. In this landmark study, Pearson and Lee found a significant correlation between spouses (0.28), showing positive assortative mating for height, but higher correlations between siblings (0.54) and between parents and offspring (0.50). Since the expected correlation between full-siblings and between parents and offspring would be 0.50 if the h^2 of the trait was 1.0, they concluded that the population variation in height was highly determined by genetic factors. These early results have been corroborated by hundreds of subsequent family studies. In populations around the world, the estimates of the h^2 of height range from 0.60 to above 0.90, clearly showing that height is a highly heritable trait.

In a review of 24 studies of parent-child correlations of height and weight, however, Mueller[31] indicated that population estimates of heritability tend to be systematically lower in developing countries than in affluent countries. There are a number of reason why this might be so. As mentioned earlier, according to classic quantitative genetic theory, the heritability of height or any trait is a function of the population in which the estimate is made, as well as of the trait itself. Heritability estimates will tend to be higher if there is positive assortative mating (i.e., a significant phenotypic correlation between parents). And indeed, assortative mating for height has been found in European or European-derived populations more frequently than in non-European populations. Also, non-European populations in the developing world tend to live under more nutritional and disease stress than European populations. In these populations such environmental factors have the potential to impact a given trait more than in affluent populations. Since heritability is the proportion of variance due to genetic influences, a larger proportion of environmentally-induced variation will reduce the heritability. Additionally, many non-European populations are experiencing rapid economic change which results in the growth environments of children differing quite markedly from that of their parents, thus decreasing parent-offspring correlations and the estimate of total variation attributable to genes.

Weight, circumferences, and skinfolds

Whereas the heritability of skeletal lengths (e.g., height, sitting height) tend to be high, the h^2 of skeletal breadths (e.g., biiliac and biacromial diameters) tend to be somewhat lower, averaging between 0.40 and 0.80. In turn, skeletal breadths tend to have higher

heritabilities than circumferences and skinfolds. It has been assumed that soft-tissue traits are more easily altered by the changing nutritional environment of individuals than are skeletal tissues which respond less quickly to changes in nutritional status, and as a result have a greater proportion of their variance explained by environmental, rather than genetic, factors.

Longitudinal studies

As mentioned earlier, the vast majority of the early literature of family studies of growth and development have been cross-sectional. In recent years there has been a renewed interest in longitudinal studies of child growth. Some of these studies have been family-based, and virtually all of these recent studies have collected DNA samples with an intent for genetic analysis. However, relatively few of these studies at this point in time have longitudinal data over the full course of childhood. And, many still do not have densely spaced follow-up visits that allow for proper longitudinal statistical modeling. Many of these limitations are due to funding constraints in the current research environment. Ideally, modern longitudinal genetic epidemiological studies of growth and development are able to use growth curve fitting methods in order to pinpoint growth and maturational events at various stages of life, particularly changes in the tempo of growth in a measure, and then examine those growth curve parameters in subsequent genetic analyses. For example, some studies[58,87] have reported high h^2 estimates for various growth parameters derived from longitudinal modeling over the course of childhood. Similarly, our research group[26,111] and others[23] have fit curves to serial infant height (length) and weight data from relatively large family samples and found significant heritabilities of various growth curve parameters ranging from $h^2 = 0.61{-}0.95$.

Maturation

Not only is physical size heritable, but the timing and tempo of maturation also are significantly controlled by genes. A number of early studies of dental development found that radiographic measures of the timing of tooth formation (calcification) and dental emergence were more highly correlated within MZ twin pairs than DZ twin pairs, suggesting a heritability of 0.85–0.90.[113] Also, the number and pattern of dental cusps were found to be under genetic control. The rate of skeletal maturation has been compared in siblings over time in several reports, with the general finding being that there is a great deal of similarity between siblings in the age of ossification onset of bones in the hand and foot. The general pattern of skeletal maturation (i.e., the tendency to be an "early" or "late" maturing individual) also suggests that the tempo of development is highly heritable, with sib-sib correlations of 0.45.[114]

The process of maturation is commonly believed to be controlled, at least partially, by genes independent from those controlling final size. This conjecture stems from the

observation that siblings may reach identical height even though they differ in the timing of maturational events.[115] Further and more widespread use of the multivariate quantitative approaches discussed in Section II, in which genetic and environmental correlations between different traits may be calculated, will allow for greater understanding of the extent of shared genetic and non-genetic factors underlying growth and development traits.

Age at menarche is one of the most studied developmental traits. A number of early studies suggested that age at menarche has a genetic basis (e.g., Boas[116]). The mother-daughter and sister-sister correlations in the age at menarche were close to 0.50, indicating a high degree of genetic determination of age at menarche. These and later studies, however, have relied primarily on recalled ages at menarche, and thus recall bias (greater in mothers than in daughters) is introduced into these estimates. Later studies have confirmed a strong genetic influence on age at menarche,[72,117] although the familial correlations were lower than in the early studies ($\sim$0.25$-$0.45). In a sample of 371 female Fels Longitudinal Study subjects of varying degrees of relationship to each other, and from whom age at menarche data had been collected during their participation in the study, Towne et al.[34] found a substantial and significant heritability of 0.49 for age at menarche.

Summary

For over a century there has been scientific interest in the genetic underpinnings of growth and development. But, as with any area of scientific inquiry, to one degree or another, all of these studies were limited by the methods and technologies available to them at the time. For that reason, most of the literature on the genetics of growth and development until relatively recently, is limited to h^2 estimates of measures of growth and development gathered once from first degree relatives. The opportunities exist today, however, for far more sophisticated genetic epidemiological studies of growth and development. One major problem, though, is that modern genetic epidemiological studies of growth and development can be expensive undertakings. Such studies are readily justified, however, on very practical and applied grounds. Foremost among these is that the growth and development of children can have health consequences later in life. Thus, to a large extent, genetic epidemiological studies of growth and development are inherently of biomedical interest. Indeed, much of the current research emphasis among modern era birth cohort studies pertains to research examining relationships between early life experiences and progression of adult chronic disease risks in later life. Placing studies of growth and development more squarely in the context of biomedical research will allow auxological investigations to move beyond being descriptive studies, and will help open the door to the increased resources needed to conduct modern genetic epidemiological studies of growth and development.

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Web site resources

General resources

Marshfield Clinic Research Institute: https://www.marshfieldresearch.org/cpmr.
GENATLAS (Database): http://www.dsi.univ-paris5.fr/genatlas/.
Online Mendelian Inheritance (Database): http://www.ncbi.nlm.nih.gov/omim.
The Genome Database: http://www.ncbi.nlm.nih.gov/sites/genome.
Genomics & Precision Health (CDC): http://www.cdc.gov/genomics/default.htm.
National Human Genome Research Institute (NHGRI): http://www.genome.gov/.
GWAS Catalog (NHGRI-EBI): https://www.ebi.ac.uk/gwas/.
National Center for Biotechnology Information (NCBI): http://www.ncbi.nlm.nih.gov/.
Genomics Science Program (US Department of Energy): https://genomicscience.energy.gov.
Wikipedia (general concepts in genetics): http://en.wikipedia.org/wiki/Statistical_genetics.
Health Sciences Library System (University of Pittsburgh): general genomics: https://www.hsls.pitt.edu/obrc/index.php?page=general_genomics.
PhenoScanner (University of Cambridge) database of genotype-phenotype associations: http://www.phenoscanner.medschl.cam.ac.uk/.

Analytical resources

Laboratory of Statistical Genetics (Rockefeller University): a comprehensive analytical resource): https://lab.rockefeller.edu/ott/.
Center for Statistical Genetics (University of Michigan): various analytical software programs: http://csg.sph.umich.edu/abecasis/.
Merlin: linkage analysis software: http://csg.sph.umich.edu/abecasis/Merlin/.
SOLAR: genetic variance components analysis including linkage and GWAS: http://solar-eclipse-genetics.org.
S.A.G.E.: statistical analysis for genetic epidemiology: http://darwin.cwru.edu/sage/.
Division of Statistical Genetics (University of Pittsburgh): various analytical resources: http://watson.hgen.pitt.edu/.
Eigenstrat/Eigensoft (Harvard University): population stratification adjustment: https://reich.hms.harvard.edu/software.
PLINK (Harvard University): Whole genome association analysis toolset: http://zzz.bwh.harvard.edu/plink/.

Data resources

UK Biobank: biomedical database containing genetic and health information from UK participants: https://www.ukbiobank.ac.uk/.
Mendelian Randomization (University of Bristol): database and analytical tools: https://www.mrbase.org/.

CHAPTER 9

Social and economic effects on growth

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Introduction

There is an extensive anthropological literature, which provides a comprehensive description of phenomenon that both human body size, in particular stature, achieved in a given age, as well as tempo of sexual maturation reveal intra- and inter-population variation. As biological features, they are determined partly by genetic and partly by environmental factors, as well as their mutual interaction. Among the environmental factors, which make a particularly significant contribution to this variation, two are foremost: quality of nutrition and morbidity on the population level.[1] These two environmental components constitute what is termed "living conditions", "quality of life conditions", or "wellbeing" of individual, family and society. Therefore, since the first half of the 19th century, in Western Europe data on the stature of children, military conscripts, and on menarcheal age have been recognized as a good indicator of the degree of social and economic deficits and resources. Moreover, they provide an indicator of the degree of social inequality in a population, and inform about temporal changes in the economic condition of the whole society or particular subgroups, precisely defined segments of the society. Since 1976, the World Health Organization has recommended using growth data of children as the best indicator of the health and nutritional status of the population,[2] and nowadays it is still commonly used by physical anthropologists and auxologists.

In 1981, prof. J.M. Tanner pointed out utility of auxological data in a social context, referring to the research area called *epidemiological auxology*, which he described with the famous sentence in 1987: *growth is a mirror of the conditions of society.*[3] The area of its inquiry lies somehow between human biology and social sciences; however, it does not concentrate on human growth per se, but rather provides growth data as a useful tool for monitoring the social and economic situation of human populations, especially groups or subgroups being at risk of poverty.[1,4,5]

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The first modern growth studies were initiated in the 1830s by Stanway, Horner and Roberton in England, and by Villermé in France,[6] and then continued by several researchers in different populations, providing data on long-term changes in wellbeing, stratification of societies and its biological consequences.[7–13] In Poland, Czekanowski[14] strongly emphasized ecosensitivity of stature as a feature. He demonstrated that small fluctuations in the differences in mean stature among the social classes of conscripts reflected subtle changes in their economic situation.

Two types of variation of anthropometric traits caused by social factors

Two main sources of variation in phenotypic traits may be distinguished: (1) intergenerational changes and (2) social gradients within a generation. Both of these categories of variation are caused by socio-economic factors.

Secular trend, which refers to the intergenerational changes in size of particular phenotypic traits at a given age, or changes in age of achieving defined stages of development (i.e. age of reaching sexual maturity expressed by *menarche*),[15–17] is a phenotypic reaction of the organism to the improvement or decline in living conditions of a given generation.[1,18–20] Secular trends can be positive with increasing size and earlier maturation, or negative. Positive secular trend has been observed in Europe since 1850, mainly based on studies of conscripts. During the past two centuries, in the Western world, including Europe, a prominent increase in average body height has been observed.[17,20–23] The mechanism underlying this phenomenon is not fully understood, but both genetic and environmental causes have been suggested.[24] The most apparent manifestation of secular trend is an increase of adult height, appearing in many places as an overgrown of parents by their children, who are taller than their same-sex parents.[20] Most often, it is believed to be associated with improved health, hygiene, socioeconomic development, increasing gross domestic product (GDP), and socioeconomic equality.[13,25,26] Secular trend is not always positive, i.e. the mean height is not always increasing in next generations. At the end of the eighteenth century, due to crop damage and high prices of cereals, children often suffered from undernutrition and hence growth deficiency, and the mean height of the next generation decreased.[27] A similar pattern was observed in Japan and European countries during wartime.[28,29] Another interesting finding is that the trend toward an intergenerational increase in body height is mainly due to an increase in the leg length, with only a small contribution of growth in trunk length.[29,30]

Social gradients can be defined as difference in given phenotypic traits, describing body size and/or determining tempo of maturation, between specific social groups in a given population (society). Most auxological studies define social groups based on socio-economic or demographic characteristics such as level of education, professional status, family income *per capita*, level of urbanization in the place of residence, and family size.

Most often, the first two characteristics are used to distinguish between "upper" and "lower" social strata in a given society. It is interesting that in Poland, where instead of a dichotomous scale for the above factors, a multilevel scale is used, such as in the case of parental education: university – college – trade – elementary school, regular gradients of average height are observed. These gradients, or social distances in mean height of 19-year-old males, appeared to be curiously constant over the 36 years between 1965 and 2001 in Poland.[31,32] Many other auxological studies on children and adolescents have confirmed a stratifying power of social factors on the parameters of growth and development.[33–37]

Social gradients in height of conscripts

Systematic studies of military conscripts conducted at the Department of Anthropology Polish Academy of Sciences between 1965 and 2010 provide the most detailed analysis of social class differences in body size over 46 years. Fudvoye and Parent[38] noted that "Poland data are maybe the most complete current conscript data available with six nationally representative samples of 19-year-old males between 1965 and 2010". This type of growth data has particularly great potential for epidemiological analysis as it combines information on both trends and gradients. This allows us to trace secular trend not only across the whole population, as intergenerational changes, but also in two or more well-defined social groups. Moreover, this type of data provides opportunity for the comparison of the intensity of trends in such specific groups and for monitoring of changes in social stratification in terms of a given biological characteristics, e.g. stature. Such monitoring of two or more successive surveys, recording several well-defined social and/or economic variables, can illustrate changes in effects of a specific social factor on growth over time, revealing changes in its "stratifying power" in the society.[1]

Here, the variation in stature of conscripts was limited to studies in relation to two factors scored on a four-point scale: (1) mother's education level and (2) level of urbanization of the conscripts' place of residence.

Among the above-mentioned socio-economic factors, the most important seems to be the mother's education level, and its significance even increased during the economic transition in Poland.[39] This indicates that even though education is positively correlated with income, the influence of maternal education level on children's growth is not entirely or necessarily caused by differences in wealth. The same financial resources available per person in the family can be managed more rationally in terms of the children's nutritional and health needs. While the father is usually the principal breadwinner, the mother is primarily responsible for the way the family budget is geared toward the welfare of children.

The level of urbanization of the place of residence seems to be a qualitatively different factor from parental education level. Rather, it reflects the extent of infrastructure development, including access to health centers, efficient public transport, access to services and shopping centers. In other words, a decline in the importance of this factor as a force differentiating biological traits informs about the decrease of these differences along the line of rural-town-city environments, and partly to decline in the environment of the urban area.

Variation in height of Polish conscripts depending on mother's level of education is presented on Fig. 9.1. In all five surveys, conducted between 1965 and 2009, there are regular gradients in mean height of 19-year-old males between four categories of this factor. However, its stratifying power has changed over time. The differences between upper- and lower categories were most pronounced in 1965 survey, then they have been diminishing, reaching in 2009, less than half the value in 1965. Although the mother's education level is the most meaningful social factor, over the course of 44 years it has been losing its stratifying power.

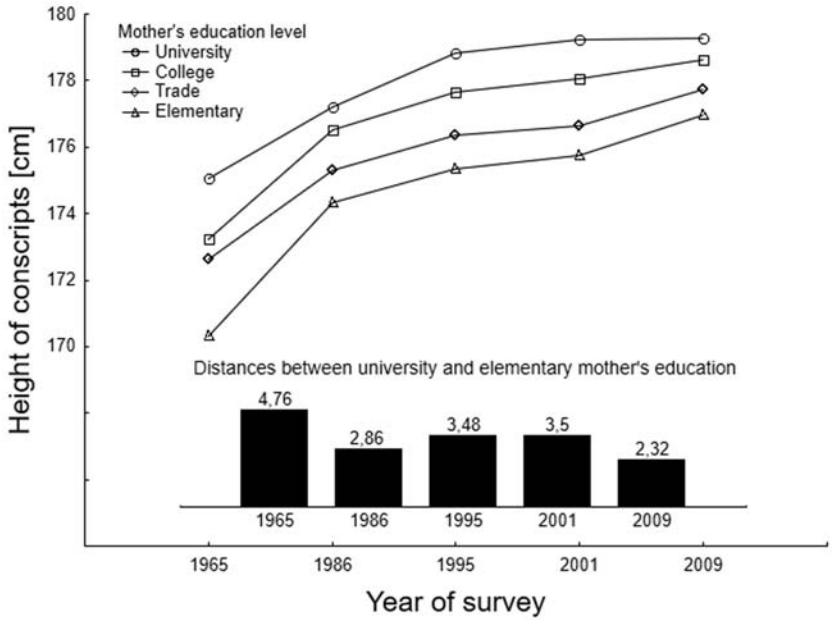

Fig. 9.1

Means of height of Polish conscripts depending on mother's education level described by a four-category scale, in five successive surveys conducted between 1965 and 2009. Lower part of graph presents distances (cm) in means of conscripts' height between two extreme categories of mother's education level.

A different picture emerges when scrutinizing the changes in variation in height of Polish conscripts on the urbanization level of residence, described by a four category scale (Fig. 9.2). First, the gradients are not regular, and the differences between city and town disappeared. Only the two most extreme categories showed marked differences in the means. However, these differences gradually diminished between 1965 and 2009 surveys. It means that over the course of 44 years, dividing the oldest and most recent surveys of conscripts, peculiarities of large urban and rural environments have become more similar. The question arises whether the living conditions in rural areas and in small towns have improved faster, or whether the living conditions of large cities populations have improved with less intensity during this time. One can answer this question by tracking the secular trend in these two specific groups. Mean height of conscripts in large cities (over 500,000 citizens), increased between 1965 and 2009 by 6.9 cm, with an intensity of 1.6 cm per decade, whereas intergenerational changes in rural areas and small towns in mean height accounted for 8.2 cm, with an intensity of 1.9 cm per decade. Thus, the inhabitants of villages and small towns made a greater improvement of wellbeing, shortening the distance to the residents of large cities.

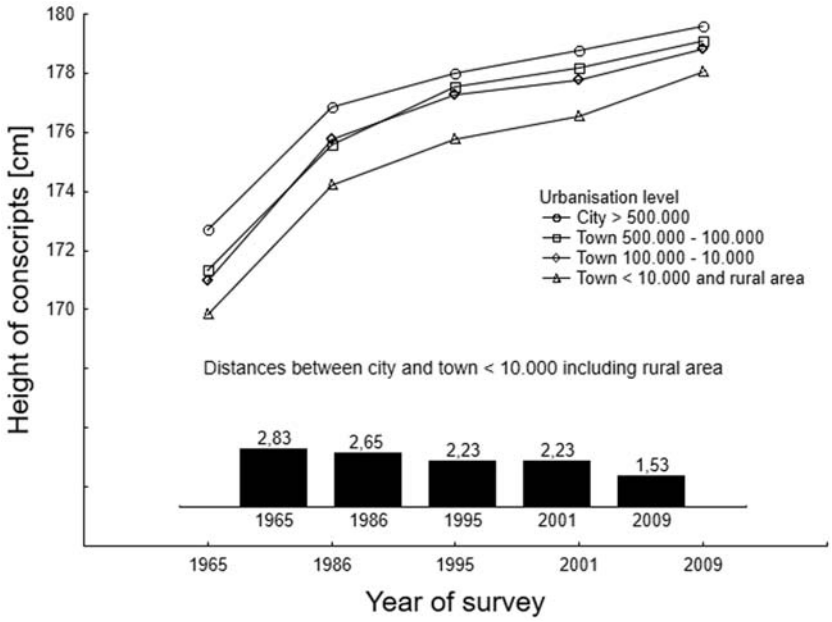

Fig. 9.2

Means of height of Polish conscripts depending on level of urbanization of place of residence, described by a four-category scale, in five successive surveys conducted between 1965 and 2009. Lower part of graph presents distances (cm) in means of conscripts' height between two extreme categories of the level of urbanization.

In most Western European countries, as well as in the USA and Canada, from 1960 to 1990 there were no significant urban-rural differences in growth status of children and adolescents.[40] During the same time, some Eastern European and Mediterranean countries, like Romania or Greece, continued to show an urban-rural gradient in growth and maturity.[1,37] However, this gradient nearly disappeared in Hungary. Conscripts' data showed that in 1973 residents of the Hungarian capital, Budapest, were taller by 2.1 cm than those of smaller settlements, but in 1998 this difference diminished to 0.1 cm and became insignificant. Based on height gain in these two groups over 25 years, conscripts from small settlements become taller by 5.1 cm, whereas city residents only by 2.9 cm. This suggests that a greater improvement in living conditions occurred outside of Budapest.[41] A similar trend in decreasing magnitude of urban-rural differences in height over approximately 30 years has been reported in boys, but not in girls, among indigenous population of the Valley of Oaxaca in Mexico.[42] Other support for this phenomenon comes from China. Zong et al.[43] have reported the narrowing urban-suburban rural disparities in the physical growth in China, mainly by sustained improvement in socioeconomic status and acceleration of urbanization process in suburban and rural areas.

Social gradients in growth of school children

Scrutinizing the schoolchildren's growth data, a similar picture of marked social stratification appeared. The presented data were collected during four Polish Anthropological Surveys conducted in 1966, 1978, 1988 and 2012 and published in Gomula et al.[37] The total random sample consisted of 63,856 schoolchildren aged 7−18 years (32,121 boys and 31,735 girls), attending primary and secondary schools of different types.[44,45] The samples were drawn from three types of localities: (1) three cities, Warsaw, Łódź and Wrocław; (2) four towns in different regions of the country (between 10,000 and 20,000 inhabitants, with a relatively stable population); (3) all villages in the county districts of these towns.

A concise summary of the results are presented in Fig. 9.3. As expected, all socio-economic factors had a significant effect on height during the studied period. However, this effect differed depending on the socio-economic status (SES) category and Survey. As regards general SES, its differential effect (toward taller children in higher SES categories, Fig. 9.1) was decreasing beginning with 1978, especially among girls, where in 2012 no significant differences between SES categories were found ($p > 0.05$). With respect to the urbanization level, between 1966 and 1988, children from cities were taller than those from towns and villages (at least $p < 0.01$). In 2012, however, these differences disappeared ($p > 0.05$). Family size also significantly differentiated height between 1966

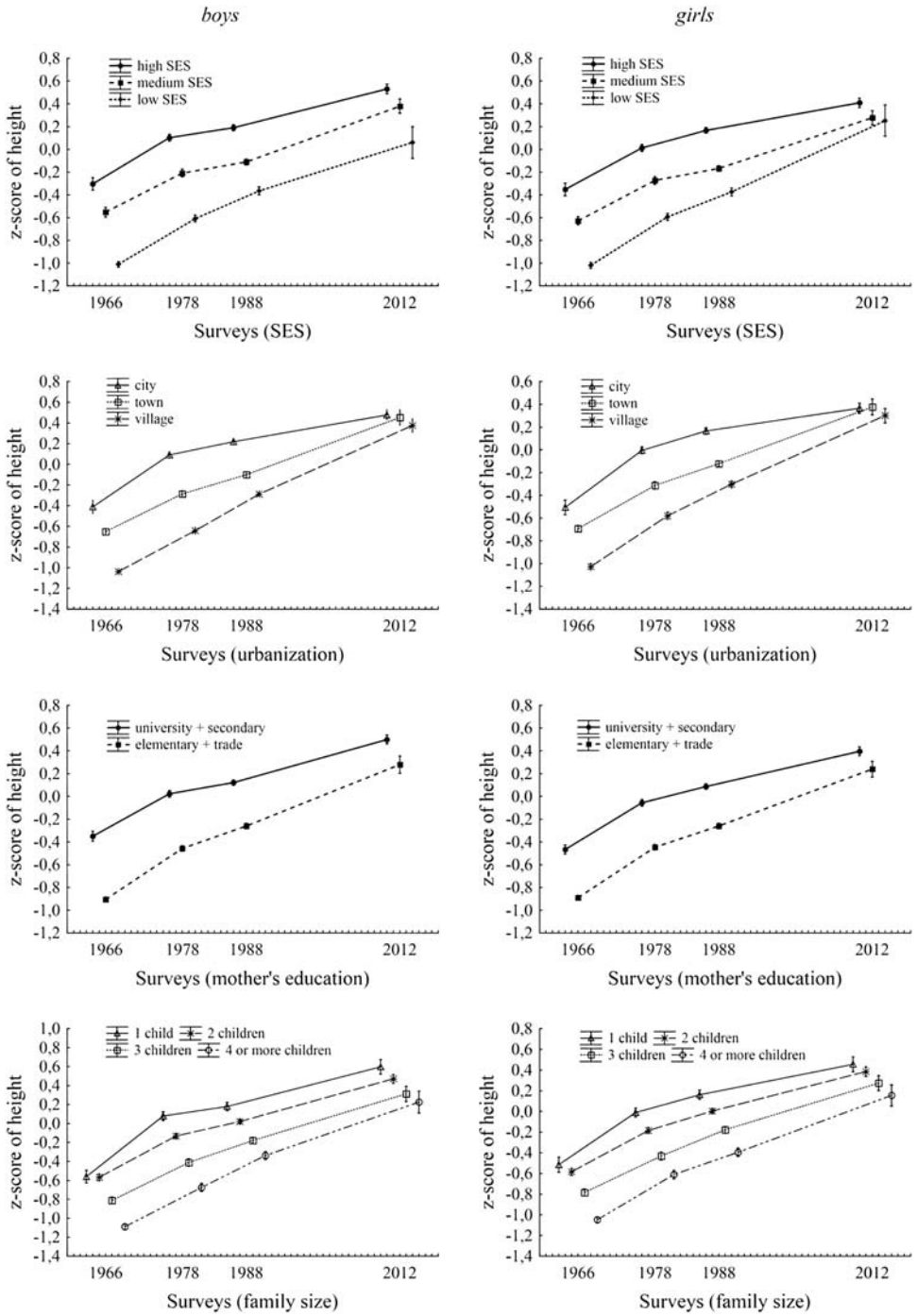

Fig. 9.3

Secular changes in body height in Polish boys and girls between 1966 and 2012, within categories of four socioeconomic factors: general level of SES, level of urbanization scored into 3 categories, mother's education level scored into two categories, and family size scored into four categories. Body height of children were standardized using LMS parameters derived from CDC (www.cdc.gov). *Source: Gomula et al.*[37]

and 1988 ($p < 0.01$) in terms of all categories (except for families with 1 child and 2 children in 1966; $p > 0.05$), where taller children were observed in smaller families. In 2012, differences between families with 1 child and 3 or more children in boys ($p < 0.001$), and families with 1 child and 4 or more children in girls ($p < 0.01$) remained significant. Although the differences in height between higher (university + secondary) and lower (trade + elementary) levels of parental education were slightly decreasing since 1978 across subsequent years, all Surveys consistently showed this difference in height, where parents with higher education had taller children (at least $p < 0.001$).

Two main conclusions can be drawn from the above description: first, all social factors have been losing their power of body height stratification in Polish children between 1966 and 2012, and second, there are some pronounced sex differences. Emphatic conformation of these regularities comes from the pattern of changes in the values of eta squared, which is a measure of effect size, or "net" effect of particular social factors, and is comparable across surveys (Table. 9.1). In all social factors, values of eta squared considerably diminished between 1966 and 2012.

Table 9.1: Eta squared values (η^2) as the measures of particular SES categories' effect size on standardized values of body height in boys and girls across subsequent years of surveys.

$\eta^2 \times 10^3$				
	1966	**1978**	**1988**	**2012**
General SES				
Boys	78.7	101.5	52.6	14.7
Girls	71.6	73.7	53.4	4.5
Urbanization level				
Boys	52.0	98.6	45.0	2.0
Girls	40.3	66.2	39.5	0.9
Family size				
Boys	51.0	66.3	29.2	13.4
Girls	45.9	48.1	33.6	8.1
Mother's education				
Boys	47.9	58.7	39.7	10.1
Girls	34.5	41.6	33.5	4.8
Father's education				
Boys	46.0	52.5	26.0	4.8
Girls	35.3	38.5	27.9	2.9

Source: Gomula et al.[37]

Social gradients in menarcheal age

A comparison of the data on menarcheal age from four Polish Anthropological Surveys conducted in 1966, 1978, 1988 and 2012 and published by Gomula and Koziel[36] indicates a downward trend. Between 1966 and 2012, the mean age at menarche declined from 13.8 to 12.9 years. Yet, these changes were not gradual and linear. Between 1966 and 1978, a significant decrease in mean menarcheal age from 13.8 to 13.09 years of age was observed, with the highest rate during the whole studied period (0.59 year per decade). During the years 1978–88, its value significantly increased to 13.27 years of age (0.18 year per decade). Between 1988 and 2012, another decline in age at menarche occurred, reaching 12.9 years of age (with a lower rate: 0.15 year per decade).

These trends were also reflected in variation of menarcheal age with respect to socioeconomic factors (Fig. 9.4). Within the particular categories of SES, urbanization

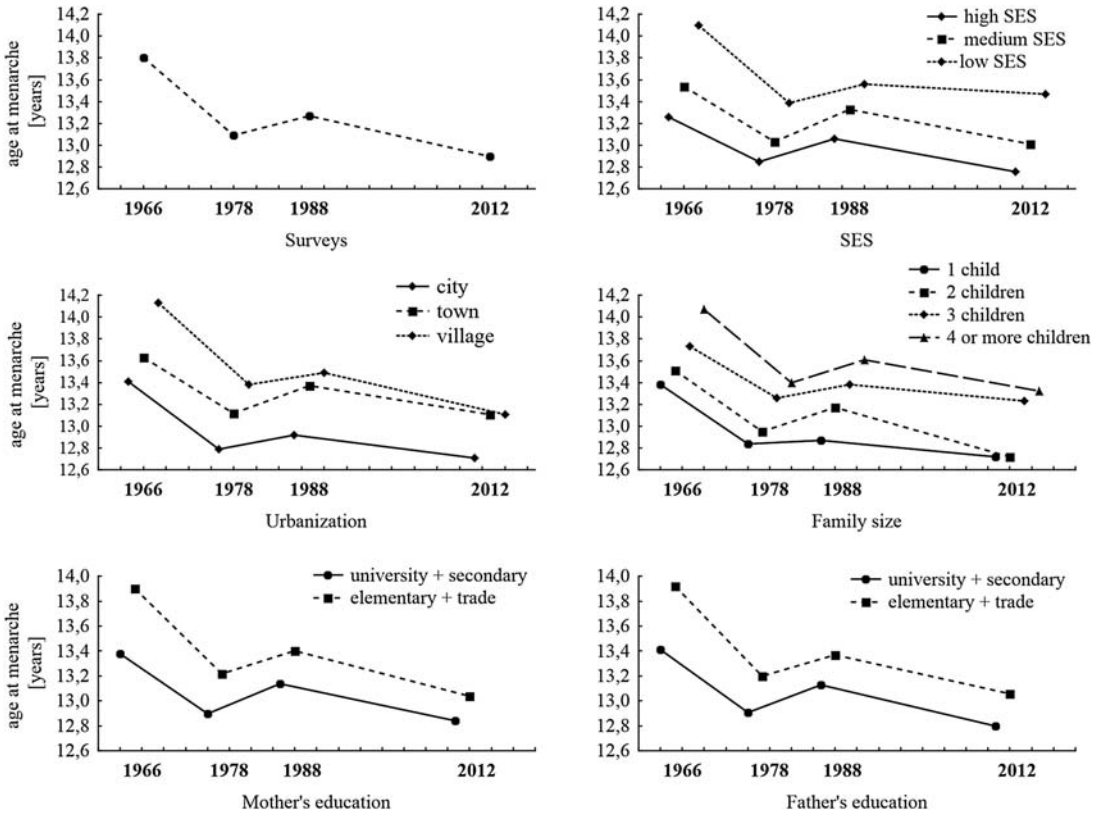

Fig. 9.4

Changes in means of age at menarche in general population and by categories of five social factors between 1966 and 2012. The means were estimated by probit analysis. *Source: Gomula A, Koziel S. Secular trend and social variation in age at menarche among Polish schoolgirls before and after the political transformation.* Am J Hum Biol. *2018;30:e23048.*

level, parental education and family size, the changes had similar patterns. During the whole studied period, the social status significantly differentiated maturation (Fig. 9.4). A constant decrease in menarcheal age variation was observed only regarding urbanization level and mother's education. Another interesting regularity was a deceleration of menarcheal age between 1978 and 1988, observed at all levels of analyzed social factors, and caused by a deep socio-economic crisis that started at the turn of the 1970s and 1980s. After relatively short period of prosperity, in the second half of the 1970s, the first symptoms of an economic slump began to appear, which was initially manifested in the sphere of investments, but gradually encompassed other spheres of the economy. After 1978, about 50% of households recorded a drop in real incomes. The negative trade balance of the country resulted in further debt to Western countries. This economic situation initiated a long-lasting economic crisis, which became the basis for the structural, social and political crisis. Since the mid-1980s, political tensions were at their peak, and economic crisis deepened.[46] All these changes were accompanied by deterioration of living conditions of families, resulting in later maturation.

Mode of action of social factors on biological features

Professional literature on the differentiating effect of social factors, such as parental education level or sibship size, on the biological parameters of growth and development of children and conscripts, although extensive and well-documented, contains a certain simplification. Many of the authors use a mental shortcut when writing about effect of social factors on biological traits, since the influence of these factors is intermediate. Namely, social factors do not directly affect biological traits but act through particular lifestyle elements, or living condition. It is commonly accepted that these elements, depending on socio-economic situation, include: harmful habits, such as smoking or excessive alcohol consumption, eating habits, and the level of hygienic behavior. These, in turn, determine the incidence of infectious diseases, the level of physical workload, and the level of psychosocial stress[31] (Fig. 9.5).

An intermediate mechanism of influence of social factors on a biological trait is as follows: social factor (e.g. level of education) − environmental stimulus (e.g. nutrition) − susceptible biological trait to this stimulus (e.g. height). In reality paths of interaction might be much more complicated and have the form of net rather than of a simple chain, mainly due to their synergic action (e.g. quality of nutrition and level of hygienic) or mutual antagonistic action (e.g. nutrition and physical workload).[31]

Are social gradients of height in the Polish population partly genetic?

It is assumed that the Polish population is ethnically, culturally and genetically homogeneous. The high homogeneity of the Polish population has been confirmed by

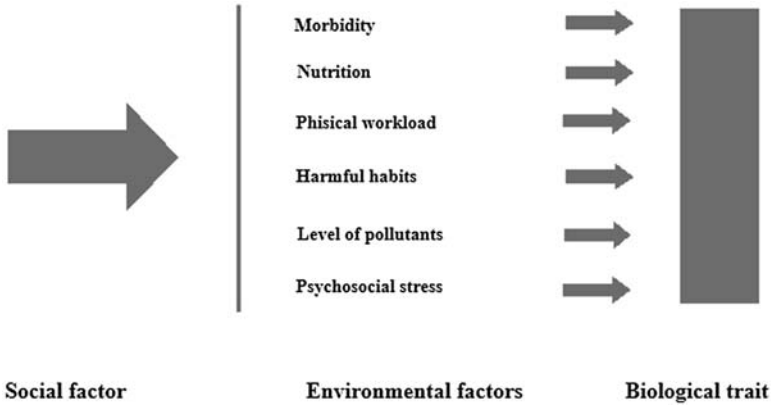

Fig. 9.5
Hypothetical intermediate influence of social factors on biological trait.

serological tests, polygenic traits and genetic studies of men from 6 different regions of Poland, based on 9 microsatellites of the Y chromosome.[47–49] In terms of simple genetic markers (allelic frequencies of several serological *loci*), as well as polygenic traits with a strong genetic determination (dermatoglyphs, iris color), respondents revealed no social differentiation, intergenerational changes, or distinct geographical gradients. Moreover, genetic studies have shown no significant molecular differences between men from different Polish regions, and the total variance accounted for mainly the variance within the population. In addition, the comparison of the Polish population with 9 populations from neighboring countries shows that as much as 9.3% of the variance of the studied genetic characteristics occurred due to differences between the populations. Furthermore, a comparison each of the six regional groups of neighboring country's populations showed statistically significant differences. These data clearly indicate not only the genetic distinctiveness of the Polish population but, above all, the high genetic homogeneity, which is probably the result of a very small inflow of foreign immigrants and ethnic mixing of the population caused by massive internal migration, as well as high social mobility and by the ethnic cleansing during World War II. It is therefore reasonable to assume that the fact that children and adults from upper social strata, determined by several factors, such as parental education level or sibship size, tent to be taller than their peers from lower strata, is a phenotypic manifestation of social disparities in living standards, at least in Poland.

It is widely acknowledged that education attainment is strongly influenced by social and other environmental factors, however a recent huge genome-wide association study (GWAS) estimated that the genetic factors accounted for at least 20% of the variation across individual number of years of schooling.[50] The authors identify 74 genome-wide significant loci associated with the number of years of schooling completed.

Single-nucleotide polymorphisms (SNPs) associated with educational attainment are disproportionately found in genomic regions regulating gene expression in the fetal brain. What is more interesting, this study suggests the acting of pleiotropy effect with height. The authors found positive statistically significant genetic covariance with height (yet small) ($P = 5.2 \times 10^{-15}$), and SNPs with concordant effect accounted for 53% (Enrichment P-value = 0.006). Those findings suggest that 53% of loci polymorphisms influence both educational attainment and height. However, meta-analysis of twin studies found that genetic influences on educational attainment are heterogeneous across countries and birth cohort, pointing out the importance role of other environmental factors.[51]

The role of inequality in society

The description of the influences of social factors on secular trend and on differences in height and sexual maturation within a society makes clear that inequality itself is a key and summarizing influence on growth and development. Inequality can be scaled in several ways. A widely used measure developed by economists is the Gini coefficient. It varies from 0 − perfect equality to 1 − perfect inequality, and when adjusted for health inequalities within a nation is a standardized Gini coefficient. Analyses have indicated that the Gini coefficient, and especially standardized Gini coefficient, are better predictors of average adult height and magnitude of sexual dimorphism in populations than gross domestic product or gross national income.[25,52] The relationship is negative: the higher the income inequality, the lower the average adult height. Sexual dimorphism is not affected by inequality and does not depend on average adult height. Based on many analyses using the Gini coefficient, one may conclude that promoting greater/higher economic equality is the most effective way to diminish/reduce the social distances in biological features and improve the well-being of the individual in societies.

Concluding remarks

The general economic situation, including social equality, is extremely important for optimal growth in a population. Therefore, socio-economic stratification and progressing inequalities in populations are one of the most important issues for politicians, as they result in the biological differences in human growth. It is well known that gradients in height reflect gradients in social disadvantage. Not only income and wealth underlie social differentiation, but also eating habits and healthcare behaviors, which are fundamental factors influencing the growth and development of children and adolescents. Height is widely acknowledged as an objective indicator of child health and a predictor of lifelong well-being in populations. Short stature is related to, e.g., enhanced risk of poor health condition and related reduction of quality of life, psychological well-being, or mortality. Children are taller, and health and wellbeing are better in countries that are more equal.[53]

Therefore, particular attention of the social policies should be paid to the most socially disadvantaged groups, especially to the large families and less educated people, to strive for a more sustainable society, where children of all social strata have equal opportunities to realize their growth and developmental potential.

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CHAPTER 10

Environmental effects on growth

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Introduction

A chief characteristic of human growth and development is that it is "eco-sensitive"; it is sensitive to a wide variety of features of the environment. Perhaps the first to establish this was Franz Boas who in 1911 showed differences among immigrant children and parents that could only be explained by the influence of the different environments experienced by the two generations. By the mid-20th century many replication studies of migrants had been conducted and the sensitivity of growth to environmental factors was established in the anthropological literature.[1] By the middle of the 20th century, which environmental factors were the most important, and their most salient influences on morphology and growth began to be tested.

The most often studied factors were features of the natural environment, and usually these were studied as extremes e.g. extreme cold or heat, aridity, high altitude, etc.[2] To these we must add *anthropogenic* features such as air pollution, metals (mercury, lead), pesticides and herbicides such as DDT, and energy (radiation and noise). Most anthropogenic factors are recent additions to our environment, and may pose biological challenges that are reflected in altered patterns of growth. Further, exposures to most environmental factors are mediated by social characteristics, making growth a response to the social environment as well as the physical one.

In studies of growth in relation to extremes of the natural environment, patterns of growth that were responses to environmental extremes, including slower maturation and reduced growth, were interpreted as adaptations, that is, relatively beneficial to the individual by providing some benefit in terms of function, survival and/or reproduction. While these benefits have been challenging to measure, the theory that growth is a way for individuals

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to adapt to their immediate physical environment and that growth responses are part of the adaptive potentialities of *Homo sapiens* is found in virtually all texts on human biological adaptation.[3,4]

More recently, the concept of *phenotypic plasticity* has garnered the interest of ecology scholars and is defined as "the ability of individual genotypes to produce different phenotypes when exposed to different environmental conditions".[5] This is a broader view in which phenotypic adaptation is only one possible result of the plasticity.

In the study of growth and development altered growth is often interpreted differently. Reduced growth and slowed maturation is often seen as an insult produced by adverse circumstances. James Tanner, who led the field of human growth and development for decades, noted the relationship between poor growth and adverse circumstances in childhood.[6] He championed the use of child growth as an index of community well-being, of health, and even of the moral status of a society as inequality of growth among different social groups reflected the unequal distribution of resources for health and well-being. He called this study auxological epidemiology as it examines the distribution among populations (epidemiology) of growth variation (auxology). In this view, slow or less growth indicates poorer health and the lack of adaptation in the face of nutritional or social disadvantage and adversity. Thus, researchers use two general and somewhat contradictory interpretations of environmentally influenced growth patterns (see Schell and Magnus for a review and discussion of the applications of these interpretations[7]).

This chapter focuses on environmental influences on growth including aspects of the natural environment and anthropogenic factors. Because of this dual focus, we will consider the contradictory interpretations of growth after reviewing the relevant data on growth and the environment.

Research design issues

Studies of growth patterns in relation to environmental factors illustrate several issues in the design of growth studies. Foremost of these is the issue of measurement. While measurement of the dependent variable, a growth dimension, is usually easily achieved, measuring the environmental factor of interest (the independent variable) is often far more difficult. In true experimental designs some participants are subjected to a controlled, measured exposure to an influence and others are not, allowing for accurate knowledge of exposure. However, most exposures of interest are negative and exposing people, especially children, in such experiments is unethical. Unless we are studying a potentially positive influence, we are left with observational study designs only and these involve unmeasured but estimated exposures.

Most studies of environmental factors examine the influence of past or ongoing exposures. In these situations, there is the issue of balanced precision, the idea that the independent variable (the "cause") and the dependent variable (the "effect") should be measured with equal precision. The earliest growth studies were descriptive and examined size (the dependent variable) in relation to age (the independent variable). Today, studies of growth and the environment require accurate and reliable measurements of both individual growth and the environmental factors, but this is not always achieved. Measuring the environment is straightforward when the environmental factor is not modified by behavior or culture and everyone living in one community has basically the same exposure throughout their lives (e.g. high-altitude studies). However, it is more difficult to measure pollutant exposures because individuals in a single community can vary greatly in level of exposure. Some pollutants leave long-term residues in the body that can be measured retrospectively to estimate past exposure, for example lead measured in blood and bone, while others leave little trace of past exposure. Exposure to energy, such as radiation or noise, leaves no trace or residue at all and this makes retrospective studies very difficult. This fact explains much of the difficulty in determining effects of cell phones that emanate microwave radiation since past radiation exposure is extremely difficult to reconstruct. Presently, the study of environmental influences on growth is limited by our ability to measure environmental factors, and the information reviewed below should be understood as a limited picture wrested from substantial difficulties measuring the environmental factors of greatest concern to human well-being.

Temperature and climate

Climate appears to influence growth and development, helping to determine body size and proportions. According to Bergmann and Allen's Rules, body size and proportions of warm-blooded, polytypic animals are related to temperature. In humans, Allen's rule predicts longer extremities and appendages relative to body size in warmer climates, shorter ones in colder climates. Bergmann's rule predicts larger body sizes in colder versus warmer climates.

There is ample statistical evidence for a relationship between adult size and shape consonant with Bergmann's and Allen's Rules. Roberts[8] examined published data on body dimensions of multiple samples of males from around the world and correlated the sample means to measures of local temperature. There is a significant negative correlation between body weight and mean annual temperature, as well as a negative relationship between sitting height as a proportion of total height and temperature (see Fig. 10.1). Newman[9] tested Bergmann and Allen's rules through examination of aboriginal males in North and South America spanning 1000 years: smaller statures are observed near the equator consonant with Bergmann's rule while the shorter legs among the Inuit is

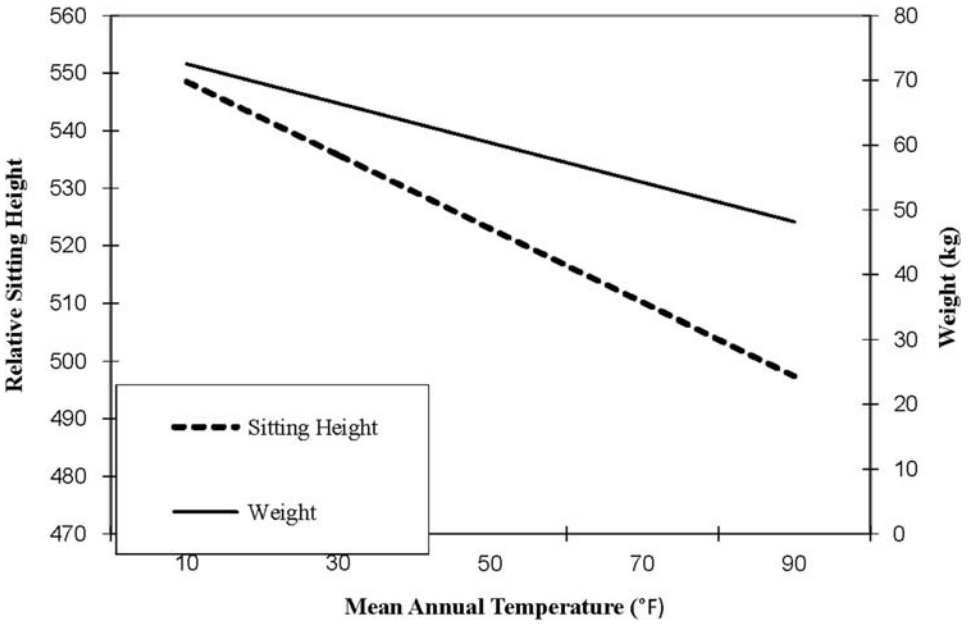

Fig. 10.1

Relationship between mean annual temperature and body weight. *Source: Adapted from Roberts DF. Body weight, race and climate.* Am J Phys Anthropol. *1953;11:533–558.*

consonant with Allen's rule. Additionally, the amount of body surface area relative to the volume of the body tends to increase from cold to hot climates.[10] An analysis of samples measured since Roberts's landmark paper of 1953 showed that temperature was still related to body size, weight to height proportions and height to torso proportions, although the relationships were weaker than in Robert's analysis. The effect moderation was due to greater weight among samples from more tropical regions which could well be due to a nutritional transition in these lands.[11] The combined effect of nutrition and temperature demonstrates how phenotypic development is the product of multiple environmental influences including ones modified extensively by social structures and related behaviors.

The relationships observed between body proportion and environmental temperature can be explained in terms of the body's thermoregulatory process. In hot, dry environments, a body that has greater surface area relative to total body size or volume will more efficiently dissipate heat produced by the body's metabolism and activity. The reverse is true for cold environments where heat retention is important to avoid hypothermia, thus less surface area through which heat would be lost is more adaptive. The small stature and low body mass of populations in tropical rainforests, for example the small tropical forest-dwellers in Africa, is an adaptive body shape in terms of the high humidity in these

environments that limits the effectiveness of sweating to dissipate heat through evaporation. The smaller body mass of these populations minimizes heat retention.[10]

The focus on the effects of temperature was primarily on adult form, and only a few studies have examined the relationships of growth parameters to temperature. Malina and Bouchard[12] suggest that the typical body shapes associated with extremes in temperature have implications for development. For example, studies of the mean age at menarche (the appearance of the first menstrual cycle bleeding during female puberty) demonstrate a negative correlation to annual mean temperature indicating earlier maturation among females in hotter climates.[8,12]

Eveleth[13] conducted a longitudinal study of well-off American children in Brazil to determine the effects of the hot climate on growth. She observed that the Rio children weighed less than well-nourished, middle class US children from Iowa, and had less weight for height, indicating a more linear body form in Brazil. Limb growth and shape illustrates this trend to linearity well. Fig. 10.2 compares the Rio boys to their North American age-mates in terms of the ratio of calf girth to length of the lower segment of

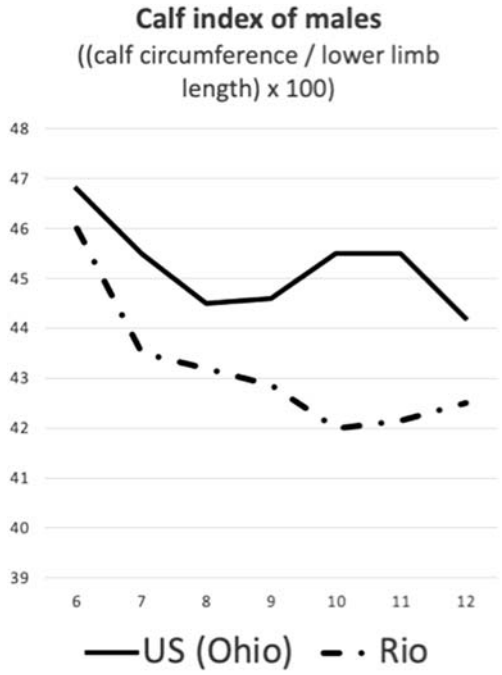

Fig. 10.2
Calf index in boys from Rio De Janeiro and Ohio *Source: adapted from Eveleth PB. The effects of climate on growth.* Ann N Y Acad Sci. *February 1966;134(2):750–759.*

the lower limb. The Rio boys have far "skinnier" calves which means more surface area to volume facilitating the dissipation of heat. This pattern of growth in size and shape is consistent with expectations from Bergmann's and Allen's rules. Age at menarche, however, did not differ between the Brazilian and US populations, indicating that the populations were maturing at similar rates. An important strength of the study of Rio children and youth is the elimination of nutritional factors by sampling high socioeconomic status children of corporate executives in an expensive private school. In addition, because the study used a longitudinal design, it is possible to see the position of the Rio youth relative to North American samples at an early age and throughout the growth period. The differences emerged early. This is consistent with work on the development of phenotypes adapted to temperature that examined the age distribution of associations between certain body dimensions (e.g. stature relative sitting height) and temperature using published means.[14] The relationships of body dimensions and temperature that were detected were seen from early ages and continued throughout the growth span. There was not one specific period, such as adolescence, when the relationship of body dimensions to temperature arose; it was present in the youngest age cohorts.

In humans, there appears to be a general relationship between climate and body size that roughly adheres to Bergmann and Allen Rules although the strength of the relationship can be modified by social factors particularly poverty and nutritional stress. The mechanisms by which climate and temperature affect growth patterns have not been intensively studied and are not well understood.

Season

Seasonal variation in growth has been observed in healthy children. In the northern hemisphere, the traditionally observed pattern among school age children was of fastest height velocity during spring or summer months while rates of weight gain are greater during autumn and early winter.[15] Height growth reaches its maximum from March through May in the northern hemisphere. The average velocity is 2–2½ times the average velocity during September through November, the period of minimal height growth.[16]

The greatest increases in weight were reported in the months of September through to November and became apparent in children after around 2 years of age.[16] These seasonal trends are apparent only in average growth velocities and are not necessarily observed in individual patterns of growth since the time in a year when the peak in growth occurs varies significantly from one individual to the next.[16] In adolescence, the seasonal patterns of growth are less clear, most likely because these are masked by the pronounced changes in growth velocity during the adolescent growth spurt.

Seasonality of growth may be a result of annual variation in sunlight or day length which influence the hormones involved in growth regulation.[10] Gelander and co-authors[17] measured monthly growth and serum insulin-like growth factor I (IGF-I) in Swedish children aged 7.8−10.8 years for 12 months. A positive correlation was observed between monthly change in IGF-I and monthly weight gain and body mass index, and a negative correlation with minor illness.[17] IGF-I also increased with increasing outdoor temperatures. Other studies have investigated hormonal influences on seasonality of growth. In the US National Cooperative Growth Study database, a subsample of pre-pubertal children with growth hormone deficiency were studied.[18] Despite receiving growth hormone therapy at a constant dose across the year, these children still displayed seasonal variation in linear growth with highest height velocity in summer compared to winter, correlating with the number of daylight hours.[18] Daily dark-light cycles influence the production of melatonin, which in turn affects the production of IGF-I and other hormones. It has also been suggested that sensitivity to growth hormone changes seasonally.[17] Thus, there are complex interactions between day length, sunlight, temperature, hormone production and hormone sensitivity; all of which may contribute to seasonal changes in growth.

The observed seasonal pattern of weight gain in well-nourished children has become less clear in studies from recent decades due to the confounding effects of school months versus vacation months, which in turn are associated with changes in physical activity, sleep pattern and duration and dietary behaviors. Weight gain has been found to be greatest during the summer vacation period for overweight children, but not in normal weight children.[19] A study of Danish children aged 8−11 years reported both height gain and weight gain peaked during spring time (January to May),[15] in contrast to patterns reported in earlier decades.[16]

In tropical and subtropical climates, changes in day length and temperature are less pronounced, but seasonal variation in rainfall is a major determinant of food production cycles, food availability and infectious disease prevalence. Height and weight growth seasonality is therefore more likely to stem from periods of sub-optimal growth due to seasonal food shortages or increases in infectious disease prevalence. Food crops and harvests vary from one geographical region to the next but pre-harvest and early harvest seasons are typically the time when food availability is lowest and food prices tend to increase, hence increases in child linear growth and weight are lowest. Similarly, infectious disease prevalence for malaria and other vector-borne diseases as well as diarrheal diseases are highest during the rainy season or monsoon, and are associated with weight losses and slowing of linear growth. In Timor-Leste, BMI z-scores of children and adolescents aged 0−19 years declined over the wet season when food resources were scarce compared to the dry season.[20] In Bangladesh, monthly longitudinal measures of anthropometry in children aged 2−6 years showed decreased upper arm circumference,

decreased height-for-age z-score and decreased weight-for-age z-score in the monsoon season (June to October); episodes of fever and diarrhea were also highest in these months.[21,22] After the main rice harvest in late October, growth rates and z-scores increased.[21] Similar patterns have been reported in many tropical and subtropical areas.

Another important contributor to seasonality of growth is the availability of vitamin D. Exposure to sunlight, which declines with increasing latitude, is essential for normal skeletal development. Ultraviolet light stimulates the production of cholecalciferol, vitamin D3, in human skin and vitamin D3 increases intestinal absorption of calcium and regulates the rate of skeletal remodeling and mineralization of new bone tissue.[23] Despite the fortification of milk in some countries with vitamin D2, the major source of vitamin D for humans is the body's synthesis of vitamin D3 under stimulation from sunlight.[23] Hence, the marked seasonal variation of sunlight in many parts of the world leads to variation in plasma concentration of 25-hydroxyvitamin D (24[OH]D), which is the best marker of Vitamin D status in plasma.[23] Vitamin D deficiency in children can lead to rickets; a disease in children characterized by poor calcification, softening and distortion of bones typically resulting in bow legs. Rickets became widely prevalent in industrializing centers of Europe in the early twentieth century when air quality was poor and working and living conditions offered little exposure to sunlight, particularly in winter months. Early treatments for rickets included sunlight exposure or UV radiation.

Seasonal variation in age at menarche has also been reported. A large study in the US reported peaks in the onset of menarche in the months of January and July, but no variation according to latitude or altitude.[24] A smaller study in Denmark reported the same peak in menarche in winter and summer, with lower than expected incidence in spring and autumn.[25] Seasonality of menarche, however, may be just one marker of the many aspects of seasonal periodicity associated with human reproduction.[24]

High altitude hypoxia

The study of growth under conditions of high-altitude hypoxia has received much attention by human biologists for more than fifty years. The studies provide insight into how growth is affected at different stages of development, the effects on different aspects of growth (proportions, fatness, etc.), and the relative impacts of ancestry, nutrition and civil strife.

Hypoxia is defined as a lack or insufficiency of oxygen reaching the cells and tissues. The degree of environmentally induced hypoxia varies with altitude. High altitude hypoxia can be deadly. Above 9000 m the partial pressure of oxygen (PO_2) is so low that it equals the PO_2 in the circulatory system. Unless the PO_2 is lower in circulation than the atmosphere, there is no pressure differential moving oxygen into the blood stream which is incompatible with life. This effect is lessened at lower high altitudes.

High altitude hypoxia is accompanied by other potential or documented influences on growth-cold stress, ultra-violet energy exposure, aridity as well as nutritional stress from shorter growing seasons and limited variety of edible plants. Add to these poverty with its usual dearth of health care resources. Of these, hypoxia is an influence that at present cannot be modified by cultural arrangements and so exert an unmitigated biological challenge. In this section the focus is on the pattern of growth. The genetic and physiological responses are best reviewed in other sources.[26–28]

Some 140 million persons live at high altitude. The highest altitudes where humans live now are Ma Gu in Tibet, and La Rinconada in Peru, both about 16,570 feet (5050 m).[29] By comparison the highest settlement in the US is Leadville, Colorado at 10,152 feet. Clearly human work and occupation at high altitudes challenges many organ systems and there is substantial evidence of multiple physiological changes that are adaptive. The pattern of growth can be responsive and possibly adaptive.

Much of our information about growth at high altitude comes from studies in just two areas: the Tibetan plateau (Qinghai-Tibetan Plateau) and populations of the Andean altiplano living in Peru and Bolivia. Responses to high altitude by these populations may differ owing to differences in length of residence at altitude and therefore length of time for genetic adaptation. Indigenous Tibetans arrived on the high plateau in paleolithic times some 30,000 years ago although permanent residence may not have occurred until 6500 BP.[30,31] Han populations migrated to high altitude Tibet far more recently. Indigenous peoples of the Andes did not occupy high altitude zones until 8000–10,000 years ago,[30] and people of European ancestry began to reside at high altitudes in the Andes less than 500 years ago.

Prenatal growth

The most significant feature of prenatal growth at altitude is a reduction in birth weight. Generally, a reduction of 50–100 g per 1000 m of altitude has been observed. Most of the reduction is due to less lean tissue.[32–35] High altitude Peruvian neonates showed reduced muscle mass compared to sea level births but body fat was similar. The effect may be altitude dependent as neonates in Leadville, Colorado (3100 m) and Denver, Colorado (1600 m) did not differ significantly in upper arm muscle or fat deposition in utero. Lean tissue growth is greatest before the third trimester whereas fat mass increases most in the late third trimester.[36] This suggests that the effect of hypoxia is pronounced well before the third trimester.

The entire distribution of birth weights at high altitude shifts downward and there are about four times more low birth weight babies born (using the standard WHO definition of a birth weight of 2499 g or less). This puts many more neonates in high risk categories needing appropriate clinical therapy if available.[35]

Placental morphology and physiology are likely to be major avenues of adaptation. Placenta's of indigenous Andean women are heavier relative to birthweight and are more often non-symmetrical in shape. These changes provide more surface area for oxygen transfer from mother to fetus.[29,37] Typically in pregnancy, blood flow through the uterine artery is increased but among most high altitude populations the flow is substantially dampened, though in some studies indigenous women demonstrate increased rates of blood flow in placental tissue associated with higher birthweights.[38–41]

There are substantial differences among populations in the extent of birth weight reduction with altitude. Births to Tibetans in Lhasa (3656 m) ranged from 450 g below the US norms to above them. The Tibetans are believed to have migrated to altitude far earlier than any other high-altitude population in Tibet. Han immigrants to Lhasa, with a far shorter history of residence at altitude, had mean birthweights over 800 g lower than term sea-level White neonates in the US. Han birth weights also were some 250–300 g below European or Aymara Bolivians.[39] The greater birthweights of Tibetans were correlated with greater maternal uterine artery flow rates and this suggests better delivery of oxygen and nutrients to the fetus.[33]

In La Paz Bolivia (3640 m), among neonates who had only European ancestors, one-third were small for gestational age (SGA) even though they experienced many socioeconomic advantages, while only 13% of neonates with only Aymara ancestry were SGA and close by were lower SES Mestizo who experienced a 16% rate of SGA.[38] Among high altitude (3000–4300 m) births in Bolivia, those with greater Aymara ancestry were taller (longer), heavier and had larger head circumferences than births with little Aymara ancestry. Differences in prenatal growth and size at birth among populations that differ in length of residence at high altitude as indexed by ancestry suggest different adaptive mechanisms at work in utero with different degrees of success.

Other dimensions of prenatal growth are affected as well. In addition to reduced birth weight, length and head circumference at birth are reduced also as are some limb lengths.[42,43] The extent of reduction in these other dimensions may vary by degree of European and Andean ancestries and while this is concordant with analyses of variation in birth weight among high altitude populations, the evidence is not consistent.[43,44]

In summary, populations at high altitude experience reductions in size at birth. Evidence for reduction in weight at birth is strong and consistent. Less work has been done on other body dimensions, but these seem reduced also. Variation in reductions are related, to an extent, to the physiological adjustments related to the delivery of oxygen and nutrients and to the ancestry of the population which may be a marker of the population's length of residence at high altitude and the opportunity for genetic adaptation to occur. However, social, economic and nutritional factors also play a role.

Childhood and adolescence

The analysis of neonatal size among high altitude populations indicates that different populations have different growth responses to high altitude. Variation in responses is due mainly to differences in (1) the altitude of each population studied, (2) poverty with its associated problem of poor nutritional status, and (3) ancestry (possible genetic adaptations).

The overriding theory regarding hypoxia's effect on growth is that it limits oxygen supplies to tissues and the limited oxygen supplies are preferentially allocated to supplying organs involved in oxygen transport at the expense of the musculoskeletal system.[27,45] High altitude Quechuan children living between 4150 and 4350 m are significantly shorter than low altitude ones at every age from two to 18 years with differences reaching 10 cm at many ages.[46] Among Tibetan children, the Sichuanese Tibetan children (3100 m) are the tallest and heaviest while the Nepalese Sherpa children (3400−3800 m) are the shortest and lightest. Stunting (height-for-age more than two standard deviations below the median of the WHO standard) of Tibetan children increases with altitude; more than 25% of children living above 4000 m were stunted indicating that linear growth is sensitive to hypoxic stress.[47] Wasting, or reduced weight-for-age is also present but is attributed to nutritional insult rather than hypoxia except among the youngest children living at altitudes above 4000 m.[47]

High altitude Tibetan and immigrant Han children differ in growth at some ages and at some altitudes. At the higher altitudes Tibetans were taller, more muscular and fatter than Han boys and girls.[48,49] High altitude Han immigrants were lighter and shorter than Han lowlanders. The larger chest growth of Andean populations was not evident among the Han.[50]

Studies of children of European ancestry in the Andes display the effects of both hypoxia and nutritional status as they are less affected by poverty and poor nutrition. French schoolchildren in La Paz, Bolivia (3200−3600 m) were 13 cm taller than their poorer Bolivian peers while still 6 cm shorter than US references. Those with the shortest exposure were nearly 4 cm taller than the children with the longest exposure suggesting a dose dependent effect of hypoxia.[51] Overall, the 6 cm may be due to hypoxia while the great advantage over the indigenous Bolivian children may be due to poorer health and particularly to poorer nutritional status Thus, while a significant portion of the growth deficit in height and lean tissue experienced by indigenous populations is due to poorer nutritional status, an independent effect of hypoxia is evident also as all high altitude populations, including advantaged ones, experience some deficit in growth.

The growth deficits are due in part to delays in maturation during childhood and this appears to be a common response in both Andean and Tibetan high-altitude children. Skeletal maturation is delayed some 20% by puberty, but by 20 years of age the difference

is nearly erased.[29] The Tibetan and Nepalese-Tibetan children are more delayed in skeletal maturation than the Quechuan children.[52]

Maturation during the pubertal years is delayed also. Among high-altitude Chinese or Tibetan populations the delay in sexual maturation may reach between 6 and 9 months while Andean and Nepalese children may delay puberty by a year or more.[53,54] Tibetan girls reached menarche at 16.1 years while Sherpa girls experienced a very delayed menarche at 18.1 years.[52] European girls at high altitude in Bolivia show a delay in age at menarche of 0.8 years in comparison to genetically similar European low-altitude girls.[54]

A smaller number of studies of growth under hypoxic conditions have been conducted in other areas and populations: Tibetan youth born in India, and Ethiopian and Saudi youth. Heights and weights of Saudi children born and raised at 3000 m were smaller than NCHS medians, while their BMI's were similar before late childhood.[55] A comparison of Indian-Tibetans born and raised at moderate to high altitudes to those raised at lower altitudes revealed similarity in height, weight and skinfolds at most ages.[56] No studies of maturation in these regions are available.

Ethiopian children grow under somewhat unique conditions compared to other high-altitude populations. There is infectious disease stress at lower altitudes that can affect growth and make comparing high and low altitude populations more complicated. The high-altitude studies in Ethiopia were conducted on the Semien highlands of Ethiopia at 3000 m which is lower than other often studied high altitude populations. In comparison to Tibetan and Andean high-altitude populations, Ethiopian children track slightly closer to US references for height and weight most markedly from later childhood into puberty. Comparing children at 3000 m to those at sea level, there were no growth differences among girls or among young boys, and only after mid-childhood were higher altitude boys taller than lowland peers. The unusual advantage of the highland boys in height may be due to there being less infectious disease stress, or better nutrition or to a genetic adaptation but none has been discovered. However, they had thinner skinfolds than high altitude Peruvian or Nepalese age peers[52] suggesting that any nutritional advantage is slight or not present. They also had substantially smaller chest circumferences for their stature than all other high altitude populations which is consistent with the more linear build of many east African populations though not conforming to the Andean pattern of greater chest growth at altitude.[52]

The slower maturation characteristic of other high-altitude groups is observed among Ethiopian children also. However, the delays are smaller, about a year by age of 12 and that is diminished significantly by age 16.[53] As with the Quechuan youth the period of growth in height and weight is extended. Ethiopian children are growing substantially at age 17 years.[52] It appears that maturation delay during childhood and even adolescence in some groups followed by catch-up is a common pattern in high altitude populations.[29]

The pattern of differences between higher altitude and low altitude Ethiopian youth reminds us that other factors can affect growth and maturation even at altitude. Low altitude Ethiopian samples are subject to growth stress from malarial infections and appear at many ages to be smaller than high altitude counterparts which is contrary from expectations if hypoxia was the sole influence. Nutritional stress coupled with hypoxic stress was associated with larger deficits in growth among Han and Tibetan children 8–10 years old living at 3100 m across both ethnic groups and between sexes. In the Andes there is considerable nutritional stress generally, but this may be more severe among the high-altitude populations. Additionally, after the early studies by human biologists began in the Andes, there was a long period of increased civil strife that reached the level of civil war in the area occupied by the Peruvian Quechuans. During this period substantial improvements in growth occurred in same altitude regions that neighbor the Peruvian Quechuans, but there is no evidence of improvement among them.[51] Hypoxia coupled with nutritional stress has substantial effects on growth and civil upheaval exacerbates the effects further. Indeed, although accurately apportioning effects of hypoxia, nutritional stress, and civil strife on growth is very difficult, many scholars believe that the shorter height and lower weight can no longer be attributed to hypoxia alone.[57–61]

In summary, reductions in weight and height at high altitude reflect the impacts of hypoxia and undernutrition related to poverty and in some cases civil strife. Growth responses to hypoxia vary with the gene pool and the opportunities for natural selection that is indirectly indicated by length of population residency at altitude. Among migrants, age at migration to altitude is influential also. While nutrition is a potent influence in these populations, the effect of hypoxia is evident clearly as well.

Changes in shape and proportion

An important feature of growth at high altitude is the change in body proportions, particularly the relative size of the chest. While chest circumference bears little relationship to lung volume among sea level populations, there is a clear relationship between chest size and lung volume with altitude. The relationship is far stronger among the Andean high-altitude populations compared to Tibetan ones.[29,48,55,56,62] Chest growth among Quechan children is dramatically greater than it is in US children of far greater stature.[29] Trunk growth early in life is greater among Quechuan children compared to European ones, and chest circumference expansion continues into the third decade.[29,54,63] Tibetan children show some differences in chest growth dimensions with chest circumference and length being greater than Han children. Children in Lhasa, Tibet who were born and raised at high altitude were similar to Andean children with short stature and shorter sitting heights, but the Tibetan children displayed smaller chest circumferences.[64] Chest length and circumference increases with altitude among Tibetan though not Han children while Ethiopian children have the most slender

chests.[32,49,55,56,62,65] Rural Aymara children have shorter legs relative to stature compared to urban age peers of European ancestry. Ancestry as a surrogate for possible genetic adaptation appears to play a role in body proportions variation among high altitude populations. Children from the Peruvian Ayacucho region (3100−4400 m) exhibited consistently smaller values for stature, head circumference, head-trunk height, total upper limb length, ulna length total lower limb length and tibia length compared to low altitude Peruvian children.[66] Interestingly, children with more Aymara surnames had shorter (1) tibial lengths, (2) relative tibial lengths (tibial length relative to stature), (3) stature, (4) lower limb length, (5) ulnar length, and, (6) relative lower limb length. These are listed in descending order of strength of association.[66] Among the low altitude children these relationships were not evident indicating that the pattern seen in the high-altitude children was not simply a characteristic of the Andean population. This suggests that the increased chest growth characteristic of this high-altitude Andean population and perhaps others, may be coupled with less growth elsewhere particularly in the lower limb and even more so in the distal limb segment.[67] This may be interpreted as a trade-off in the facilitation of growth at altitude. Similarly, one study of rural Aymara children found them to have shorter legs relative to stature compared to urban European ancestry children of the same ages.[68] There also are changes in the proportions in other populations although the changes do not follow the same pattern. Tibetan children have longer lower legs compared to Han peers and Han children with the greatest lung volume (forced vital capacity) had leg proportions like Tibetans. This suggests that greater forced vital capacity allows greater growth of the lower leg, a segment that has been seen as affected by growth insult earlier than other effects on linear growth.

Thus, while both indigenous and immigrant children ultimately produce larger chests and higher lung function than lowland peers, indigenous growth responses begin earlier and remain more profound. These increases, taken with enhanced lower leg growth, appear to be signature adaptive responses in body shape and proportion to hypoxia alone.

In summary, growth under hypoxic conditions follows different patterns in different high-altitude areas although there are some features that are common. Shorter stature and maturational delays have been observed in many studies. An extended period of growth and shorter lower limbs relative to stature are also observed in several populations. Quechuan children demonstrated very expanded growth of the chest, far more so than other populations. The variations relate to different genetic and physiological adjustments to the stressor as well as the imposition of other insults, most notably nutritional ones.

Pollutants

Pollution is usually defined as unwanted materials (e.g. lead, mercury, particulate matter), or energy (e.g. noise and radiation) produced by human activity or natural processes such

as volcanic action. The "unwantedness" is usually based on suspected or documented effects on human health or effects on the environment. Anthropogenic material pollutants are produced from power plants that generate energy, manufacturing industries, transportation, the construction of homes and factories, and agriculture. Once created, pollutants are dispersed globally to virtually all populations by wind and water currents, and through the food chain. While we tend to see pollutant exposure as a feature of environments in well-off industrialized countries, pollutant exposure also occurs in less well-off countries through cooking and heating fires, herbicides and pesticides used in agriculture, contamination of the food supplies and even in mini-industries reclaiming and recycling components of technology cast aside by well off countries.

In the past most of our knowledge of biological effects of pollutants came from occupational studies. These usually documented the effects of large exposures on adult males and did not consider children and pregnant women who are now viewed as the most vulnerable segment of the population. Further, most people are exposed to low doses, casting doubt on the generalizability of exposure standards based on occupational studies. Due to developments in measurement technology, it is now possible to make accurate measurements of low levels of pollutants using very small bio-samples. Pollutants are now routinely detected in pregnant women, newborn babies, and children, and we need to understand their effects on the developing organism when environmental insults can have irreparable, long lasting effects. Fetal programming (see chapter 2 on prenatal growth), the impact of environmental factors on the fetus that affects its functioning postpartum and its health in later life, can be thought of as a reformulation of reproductive toxicology that includes nutritional insults as well as chemical ones.

The study of human development and toxicants is based on observation of existing situations only. True experimental work in which exposure is randomized to subjects is obviously unethical. Purely observational studies yield statistical associations and each of these must be judged in terms of the likelihood that the association has a biological cause. Hill's criteria are a set of criteria for evaluating the causal basis for a statistical association. Six of these are commonly used (see Table 10.1). Studies of growth and environmental factors should be designed to meet these criteria as much as possible.

All of the listed criteria depend on the accurate and reliable measurement of exposure. The best way to assess exposure is to measure the pollutant of interest in the person. For

Table 10.1: Commonly used criteria for judging the causal basis of statistical associations.

1. A strong statistical association
2. Biologic credibility or plausibility to the association
3. Consistency with other studies
4. Compatible sequence of cause and effect
5. Evidence of a dose-response relationship

example, in a study of lead, it is best to measure lead in the blood or bone. An inexpensive but far less accurate method of assessing exposure is the substitution of a measurement made in a geographical zone, such as a postal zone, for the exposure of every child living in the zone. However, people in one zone are likely to experience different amounts of true exposure and grouping them together and using an average value leads to misclassification. This produces large errors in the independent (exposure) variable and less statistical power to detect effects. Too often studies of growth and pollution are forced for economical reasons to use this latter method, but effects on growth are more likely to be accurately determined if we can employ the most accurate measures of exposure. Despite the challenges in studying pollutants, there is now considerable evidence that human physical growth and development is sensitive to several pollutants including lead, the components of air pollution, organic compounds such as polychlorinated biphenyls and DDT (DDE), as well as some forms of energy such as radiation and noise.

Cigarette smoking

Cigarette smoking is a perfect example of an anthropogenic influence on growth and development. Exposure is a function of human behavior, the exposure composition is complex, and human experience with smoke is fairly recent, although some could argue that smoke is the oldest pollutant.[69]

Cigarette smoke contains a large variety of compounds including carbon monoxide and cyanide. These compounds can cross the placenta and affect the fetus, and second-hand cigarette smoke may affect children in households with smokers. Postnatal exposure to cigarette smoke may also affect growth, but this problem has not been studied sufficiently.

After length of gestation, maternal cigarette smoking is the single greatest influence on birth weight in well-off countries.[70] Women who smoke during pregnancy have babies weighing on average 200 g less than babies of non-smokers. The amount of reduction depends on the number of cigarettes smoked during a pregnancy. Where the average rate of smoking is less, the impact will be less. In most populations suffering from nutritional stress, very few women smoke during pregnancy, so the effect of smoking is minimal or absent.

The dose-response relationship between exposure and reduction in birth weight is good evidence for a causal relationship between smoking and prenatal growth (see Table 10.1). Gestation length is reduced by only 2 days or less which cannot account for the birth weight decrement. When birth weights of smokers' and non-smokers' infants are compared at each week of gestation from weeks 36 through 43, smokers consistently have lower mean birth weights. Just living with a smoker may affect birth weight, as women whose husbands smoked had lower birth weight babies.[71]

The reduction in mean birth weight is part of a downward shift of the entire distribution of birth weights. Thus, the frequency of LBW is approximately doubled among smokers.

Maternal smoking also is significantly associated with shorter body lengths (about 1 cm), reduced arm circumference and, in some studies, slightly reduced head circumference.[72–76] However, adipose tissue is not reduced by maternal smoking during pregnancy.[73,77]

The sizes of the decrements evident at birth depend on the amount and timing of cigarette consumption by the mothers in the sample. As prenatal weight growth is greatest in the last trimester, it is strongly affected by smoking then. Quitting before the fourth month of pregnancy is thought to reduce or remove the effects of smoking on birthweight.[78] However, quitting is more common among light smokers than heavy smokers, confounding the effect of dose with the effect of quitting or reducing. When both the amount of smoking and the quitting is considered, very heavy smokers (30+ cigarettes per day) who quit may not fully lower their risk of delivering a lighter baby.[79] In studies of more moderate smokers, quitting for the duration for the pregnancy is associated with odds of low birth weight and mean birth weight that are equal to those of non-smokers.[76,78] In one longitudinal study using repeated ultrasound imaging, biparietal diameter of the head increased significantly faster among fetuses of non-smokers from the 28th week of gestation onwards, and in another study biparietal diameters of fetuses of smokers were smaller when measured at 24 weeks, i.e., starting just before the last trimester of pregnancy.[80,81] Among mothers who smoke, fetal growth trajectory shows early signs of deflection indicating that the effect of cigarette smoking is not confined to the last trimester and some effects on prenatal growth may be caused by altered placental development. However, from a practical point of view, quitting or reducing smoking is advised for all women who smoke and who are pregnant or who may become pregnant because smoking has such a strong, detrimental effect on the fetus. It should be noted that passive maternal exposure to cigarette smoke is associated with reduced birth weight also but to a lesser extent than maternal smoking itself.[82]

For many years a debate existed on the cause of reduced birthweights with reduced appetite and lower maternal weight gain often cited as the cause of the reduction. However, careful studies analyzing strata of maternal weight gains showed that the birth weight reduction occurred at all levels of maternal weight gain. The finding that subcutaneous fat thicknesses are not reduced in births to mothers who smoke, also suggests that maternal nutritional deficiencies are not responsible.[73,77] The primary constituent of tobacco smoke is carbon monoxide. Carbon monoxide, with an affinity for adult hemoglobin 200 times that of oxygen, has an even greater affinity for fetal hemoglobin. It is estimated that if a mother smokes 40 cigarettes per day there is a 10% concentration of carboxyhaemoglobin equivalent to a 60% reduction in blood flow to the

fetus. Thus, cigarette smoking exacerbates fetal hypoxia which has some similarities to high altitude hypoxia. In fact, in some studies placenta ratios are larger among smokers largely due to the reduction in birth weight, as they are among high altitude births. Some studies have noted that the placentas of heavy smokers are heavier than non-smokers' placentas,[83,84] a finding consistent with effects seen at high altitude.[37] However, other studies have found no difference in placenta size or a reduction in size associated with heavy smoking and the nicotine content of cigarettes smoked[74] and one found that placentas of women who quit smoking by the fourth month were slightly larger than those of nonsmokers.[78] Smokers' placentas are thinner with larger minimum diameters.[83] Some of these changes in placental morphology may be adaptive given the reduced oxygen carrying capacity of the blood, but other changes (e.g. calcification) or ones indicative of aging or chronic ischemia (lack of blood flow) in the placenta do not appear to be adaptive.

Cigarette smoke also contains nicotine, which stimulates adrenal production of epinephrine, norepinephrine and acetylcholine, and this results in less blood flow through the uterus and placenta. It also can act on the fetus directly to increase fetal blood pressure and respiratory rate. In addition, cyanide, lead and cadmium are contained in cigarette smoke and are all toxic.[85] Smoking can also affect hormone levels in men[86] and if similar effect occurs in women, this in turn could affect prenatal growth.

Postnatal effects of cigarette smoking are less well studied and less clear. Follow-up studies of smokers' offspring have difficulty separating effects that may develop from being exposed to cigarette smoke in utero from the effects of postnatal exposure from living with adult smokers. Ideally, to research the effect of postnatal smoking, one would study children whose mothers did not smoke during pregnancy but who began smoking soon after giving birth. Few mothers meet these conditions leaving most researchers to study children whose mothers smoked during pregnancy and who have continued to do so after the baby was born. Though some studies have not found lasting effects from birth many other studies do. The difference may be due to the extent to which other influences on growth are controlled or to the size of the sample. Using a sample of a few hundred children, Hardy and Mellits[87] found a 1 cm difference in length at one year of age that, though small, was statistically significant, but no differences at 4 and 7 years of age. In studies using larger samples, differences in height of about 1.5 cm at age 3 years[88] and at 5 years of age[89] were found. One study using cotinine as a marker of smoke exposure found nearly a half standard deviation unit decrease in length at birth, 3, 36, and 60 months of age.[90] Analysis of the National Child Development Study, which is a very large national sample, detected a deficit of approximately 1 cm in children's heights at 7 and 11 years associated with maternal smoking, and at 16 years as well but only in male heights.[91,92] In another study of 3500 adolescents, the heights of 14 year old girls were reduced by an average of nearly 1 cm, which was statistically significant, but the boys'

heights did not differ significantly.[93] It seems that the difference of 1 cm that is present at birth becomes a smaller fraction of the variation in height that increases as individual differences in the tempo of height growth are expressed and reach their greatest magnitude at puberty. Maternal smoking also has a number of other effects in the offspring including altered neurological development, stress response and cognitive status in childhood and adolescence.

The effect of passive smoking is small but significant in large samples. Rona and colleagues[94] examined the heights of children in relation to the number of smokers in the household (none, 1 or 2) and corrected for birth weight to remove effects of maternal smoking during pregnancy. Height declined with more smokers in the home suggesting that passive smoking may affect postnatal growth.

A study conducted before the obesity epidemic began found that skinfold thicknesses of 6–11 year old children were reduced in relation to maternal smoking.[95] This finding is consonant with observations among adults that smokers are leaner[96] and their fat distribution tends to be more centralized (located on the torso).[97] This, in turn, is consistent with the observation that cigarette smoking contains anti-estrogenic compounds such that female smokers tend to have fat patterns that resemble those more typical among males. The difference seen in 6–11 year-old children may be a late expression of an effect of prenatal exposure, or may be a response to postnatal exposure to cigarette smoke. However, recent studies have found associations between tobacco smoke exposure and overweight and obesity.[98]

There is no doubt today that cigarette smoking is a powerful cause of reduced prenatal growth. Deficits are greatest in weight at birth but these appear to be made up during childhood, while the small deficit in length is not. Postnatal exposure to second-hand cigarette smoke seems to reduce height growth slightly, though more replication studies are needed. However, all studies of growth in relation to any factor should consider the effects of exposure to tobacco smoke, especially if the subject is the growth of the fetus.

Air pollution

Air pollution is a ubiquitous form of pollution and a very heterogeneous category of materials as it typically includes oxides of nitrogen and sulfur, ozone, carbon monoxide and particulate matter of different diameters (PM10 − PM2.5) as well as other site-specific chemicals. Studies in which air pollution levels are measured on the individual level are rare. Most studies compare two or more settlements that differ in the severity of air pollution and many control well for differences in socioeconomic status.

The effect of air pollution begins prenatally. An early study of birth weight in Los Angeles, California found that weights decreased in relation to the severity of the air

pollution, and the effect was evident after controlling for some of the other large influences on birth weight (mother's cigarette smoking and socioeconomic status).[99] This finding has been well replicated in numerous studies with very large sample sizes,[100–102] but there also are a few instances where no effect has been found.[103,104] The amounts of birth weight reductions tend to be small, less than 10 g typically, though some studies find far larger reductions; the distribution of birth weights is shifted downward so the increase in the odds of a preterm birth is often near 10%.[105,106] A study of births in London, UK, found that 3% of term LBW cases could be attributed to residential exposure to higher levels of airborne fine particulate matter during pregnancy.[107]

Most studies use measurements of air pollution outside the home but indoor air pollution is a factor also. Indoor air pollution created by fires for cooking and heating have been found to affect growth,[108–110] and chemicals outgassing from treated furnishing or construction materials (e.g. formaldehyde) can affect prenatal growth.[111] Specific industrial chemicals released from manufacturing sites can affect prenatal development increasing LBW frequency.[112] Clearly the specific constituents of air pollution influence the effects.

Variations in results have numerous causes: variation between studies in the components of air pollution and their levels; methodological differences in exposure measurement; when the exposure occurs during the pregnancy; definitions of outcomes such as low birth weight and small for gestational age; and control for other influences on birth outcomes.[105] A systematic review found consistent evidence of an association between preterm birth and exposure to carbon monoxide, exposure to nitrogen dioxide (NO_2), and small diameter particulate matter (PM2.5).[105] Even low levels of exposure to air pollution (PM10, PM2.5, NO) are associated with preterm birth and low birth weight.[106,113–116] The most recent work has tried to determine what components of air pollution may be responsible, the suspended particulate matter of different sizes, or the gases (carbon monoxide, sulfur oxides, nitrogen oxides and ozone) and many of the papers cited here scale effects to different components of air pollution. However, as air pollutants tend to occur together, albeit often in different proportions, there is variation in effect sizes per pollutant. The impact of different times of exposure during the pregnancy is difficult to estimate because most exposure to air pollution is chronic and the levels at different times tend to be very similar.[114,117,118] However, some opportunities arise fortuitously. During the 2008 Beijing Olympics, the government imposed very strict air pollution controls. When the Olympics occurred during the eighth month of the pregnancy, the births averaged 23 g greater than births occurring during the same months in 2006 and 2007 when there were no special air pollution controls.[119] In short, there is a small effect of chronic exposure to polluted ambient air on birth size. Though the effect on an individual birth is small, the number of persons exposed is in the millions.

There are far fewer studies of postnatal development in terms of air pollution. Almost all report that height and weight growth is more favorable in the less polluted areas though not all do.[120–122] Some studies focus on smoke from biofuels and find reduced height.[123,124] Overweight or obesity is often reported as greater in children exposed more to air pollution,[125,126] and while there are many studies of overweight and obesity, none report effects on height and weight separately making it impossible to discern if the effect on BMI is from lower heights or greater weights or a particular combination. Slower skeletal maturation has been observed in some studies.[127,128] It is possible that air pollution exerts an effect like high altitude hypoxia, limiting the oxygen available for growth. Mikusek[129] found that girls from an air polluted town were delayed in all growth dimensions except chest development, a selective effect similar to the sparing of chest circumference growth seen in some studies of high altitude Andean children.

In summary, numerous studies have found reduced fetal growth in relation to components of air pollution. The size of the effect is usually small, 10 g or less. Similarly, although there are far fewer studies of postnatal growth, these also find small effects. However, because of the ubiquity of air pollution, the total effect is large. Further, when distributions of birth weight or postnatal heights are shifted downward in a population of millions affected by air pollution, the number of individuals falling below clinical cut-offs, e.g. stunting or low birth weight, increases greatly.

Organic compounds: PCBs, DDT/DDE, PBDE, phthalates

Organic pollutants include many insecticides and herbicides that have been used in agriculture and pest control. DDT (dichloro-diphenyl-trichloroethane) is a pesticide, highly effective in controlling mosquitos, that was banned in the US in 1972. However, it is not easily broken down and is stored in the body as DDE, chiefly in adipose tissue. It persists in the environment as well. Its' metabolite (DDE) can be detected in most populations. Other pollutants were manufactured for use in various industries (e.g. polychlorinated biphenyls, phthalates), and others are unintended by-products of manufacturing, such as dioxin. Phthalates are plasticizers used in bottles, toys, and personal care products. PCBs (polychlorinated biphenyls) are a large group of similarly structured compounds that vary in toxicity and persistence in the environment and in the body. Each form (or congener) of PCB is identified by a number (e.g. IUPAC #180). Some forms are very similar to dioxin. PBDEs (polybromated diphenyl esters) are fire retardants added to a large variety of consumer items that leach into surrounding materials and now can be detected in many populations. Organic pollutants such as PCBs, dioxin and DDT are lipophilic; they are stored in fat cells and they can be retained for years. They cross the placenta easily, and are transferred through lactation. They are also found in dietary items such as fish, meat and dairy products and in human populations around the world.

PCBs may affect endocrine function, physical growth, maturation and/or cognitive or behavioral development of children and youth. Evidence of the effects of PCBs in humans comes from two types of studies: studies of acute poisoning, either food poisoning or an occupational accident, and studies of chronic low-level exposures, usually from ingestion of foods with slight but measurable contamination.

An acute exposure occurred following ingestion of rice oil contaminated with a mixture of PCBs, dioxin and dibenzofurans poisoned thousands of adults and children in Japan in 1968 and in Taiwan in 1978–79. The exposure produced diseases called Yusho and Yucheng, respectively. Yusho/Yucheng infants have had higher rates of mortality and lower body weights at birth.[130] Yucheng babies were 500 g lighter at birth than controls.[131] Even children born well after their mothers were exposed to the contaminated oil were more often born prematurely and small at birth; the difference became less pronounced the greater the time between exposure and birth.[132] The long-lasting effect of maternal exposure is most likely due to transplacental transfer of any toxicant that had been stored in maternal adipose tissue. Reduced postnatal growth also characterizes Yusho/Yucheng children; at age 7 years they were 7% lighter and 3% shorter than controls.[131,133]

Studies of children born to women exposed to smaller amounts of PCBs over a long period of time have also found growth deficits. A common but not universal finding is that birth weight is reduced in response to PCB exposure by as much as 400 g although the type of PCBs influences the effect.[134–137] The effect seems be due to less growth during gestation and not prematurity. Head circumference may be reduced also.[137]

Dioxin and dioxin-like compounds are also related to reduced birth weight.[138,139] PCB levels and body mass index are related early in life[140] and at puberty.[141] DDE, a metabolite of the insecticide DDT, has been related to reduced birth weight and height in several studies,[142] but with increased height and weight for height in others.[140,141,143] Some phthalates or their metabolites have been associated with size at birth and postnatal growth as well.[144–147] Polybromated diphenyl ethers (PBDE) also are associated with lower birth weights in some studies but not all.[148,149]

It is important when interpreting conflicting results to account for differences in exposure among the studies. One would expect a smaller effect or none at all when the exposure is very low. However, comparing exposure levels among studies is not straightforward because techniques for measuring compounds have changed over time and even now laboratories differ in which congeners are measured best. In addition, different effects may stem from differences in the timing of exposure: prenatal versus postnatal and as these compounds can disrupt the endocrine system, different effects in males and females are expected.

Overweight and obesity may be affected also. A review of the literature found low level exposure to PCBs or and DDE is associated with greater measures of adiposity while studies of samples having much higher levels find negative associations.[150] This is one example of a curvilinear relationship between a pollutant and an outcome. Other organic toxicants have been associated with measures of adiposity and diabetes including bisphenol-A and tributyltin and to a lesser extent, some of the perfluorinated compounds.[151]

Clearly all studies of humans do not agree as to the size and direction of effects that these toxicants have. This creates questions about the influence of differences in levels of exposure, differences in the timing of exposure (prenatal/postnatal) and differences in the mixtures of compounds to which the sample was exposed. Excepting occupational exposures, mundane exposures tend to be to a mixture of several compounds. While we tend to group all these persistent organic pollutants as "toxic", we have learned not to expect them to have similar effects on growth as different compounds act on and through different physiological pathways. We also have learned that measuring exposure is different from measuring body burden. Current body burden depends on whether the toxicant is persistent and stored for years or decades thereby providing a good summary of past exposure (e.g. PCBs, lead), or is rapidly metabolized and provides little information of past exposure and insult (e.g. phthalates).

We do know that the alterations in growth are best explained as due to interference with hormonal signaling. Many studies of non-human animals have shown that hormone activity can be altered following exposure to PCBs and other organic compounds. Thyroid hormone signaling is especially important for normal physical and mental growth and development. Neurological effects are among the most consistently reported effects of chronic PCB exposure. A study of Mohawk adolescents, 10−17 years of age, found the combination of reduced thyroxine levels and increased TSH levels (this usually signals low thyroid activity) in relation to levels of persistent PCBs that reflect past exposure, but not in relation to PCBs more reflective of current exposure. This suggests that prenatal or neonatal exposure may be influential.[152]

Many types of organic pollutants structurally resemble sex steroids as well as thyroid hormones. The possibility of deranged hormonal signally of sexual development and reproduction has been a controversial area of research, but there is now sufficient evidence that it occurs in humans. Several studies conducted by different research groups and with different populations have reported that exposure to some pollutants accelerates the development of puberty while others have found delays illustrating again that the type of toxicant makes a difference. Replication among studies is difficult as different samples have exposure to different combinations of compounds and at different times of development. An excellent, illustrative example of the diverse effects of toxicants on

sexual maturation comes from a study of boys in Russia.[153] In this careful longitudinal study of nearly 500 boys, the level of dioxin and dioxin-like compounds in the blood was related to delayed sexual maturation while the level of non-dioxin like compounds was related to earlier maturation (Fig. 10.3). Again, not all toxicants act physiologically in the same way.

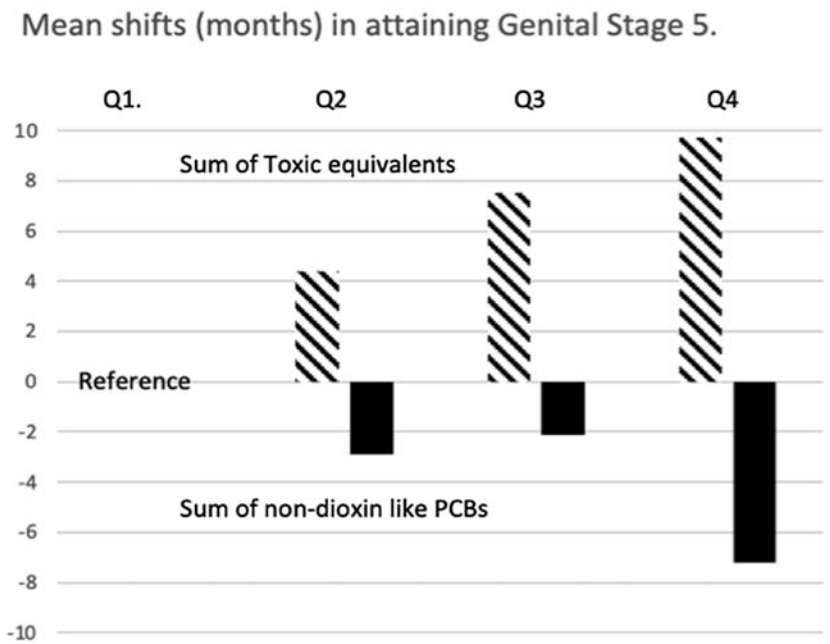

Fig. 10.3

Sex maturation of boys showing delay by dioxin and acceleration by non-dioxin compounds. *(Source: adapted from Burns JS, Lee MM, Williams PL, et al. Associations of peripubertal serum dioxin and polychlorinated biphenyl concentrations with pubertal timing among Russian boys.* Environ Health Perspect. *2016;124(11):1801–1807.*

Whether the effect is induced by prenatal or postnatal exposure, or both, is not clear. Newborns were found to have significantly lower testosterone and estradiol levels in relation to their mothers' levels of dioxin, dibenzofuran (similar to dioxin) and dioxin-like PCBs.[154] Follow up of boys in the Yucheng cohort who had substantial prenatal exposure to dioxin-like compounds showed reduced testosterone levels and increased FSH levels but no difference in Tanner stage.[155] Preliminary results from the same cohort found significantly reduced penile lengths, a possible effect of their exposure prenatally when critical sexual differentiation and development is occurring.[156] This effect has been replicated. Adolescents of the Akwesasne Mohawk Nation who were likely exposed to PCBs both prenatally and postnatally found lower testosterone levels in relation to PCB levels and a similar relationship was found among adult men who probably were exposed postnatally.[157,158]

A new pollutant of concern is a related, lipophilic compound, PBDEs (polybrominated diphenyl ethers). This is a class of fire retarding chemicals used widely in fabrics, furniture foam padding, wire insulation, rugs, draperies, and upholstery and plastic cabinets for appliances. In adult men it has been strongly and inversely associated with a measure of androgen, with luteinizing and follicle stimulating hormones and positively with inhibin B and sex steroid binding globulin.[159]

These results and others like them strongly suggest that chemicals in our environment can affect levels of hormones directly involved in reproduction and development. In true experimental studies of non-human animals, endocrine disruption is clearly evident and this establishes the biological plausibility of the associations seen in observational studies of human populations.[160] Research on children and PBDE is just beginning. If the effects seen in adults are present in children, they certainly could affect growth and sexual maturation. Other chemicals that can be found in drinking water (trichloroethylene, tetrachloroethylene and benzene) have been associated with reduced size at birth as well.[161]

The literature indicates that there is sufficient evidence to be concerned about organic toxicants because of their effects on the fetus and children. Concern about effects in humans is justified by work with animal models. The controlled laboratory studies of higher primates and rodents show reductions in growth and alterations in sexual development.[162] We know that high exposures of humans, such as those from food heavily contaminated with organic toxicants such as PCBs, produce predictable effects. Now studies show that low level exposures can affect child development, and the possibility that the fetus is especially sensitive, even at low levels, is borne out by many studies of effects on size at birth.

Lead

Lead has been a common pollutant since it was first added to paint and gasoline 100 or more years ago. In the US, lead burdens are higher among urban, disadvantaged, minority children because of their residence in poorer areas with dilapidated housing with flaking leaded paint and with older roadways where for decades cars burned leaded gasoline that expelled lead particles that landed on nearby grounds. People also are exposed to lead from their mothers through transplacental passage and lactation. Lead is a legacy pollutant that has been transmitted to each generation through biological pathways and socially constructed environments of risk.

Studies almost always find that size at birth is reduced and gestations are shorter with increased lead exposure even when the maternal lead levels are quite low, although the degree of control for confounding variables, such as maternal nutrition, can affect

findings[163,164]. Other studies have found reductions in head circumference. A study of 43,000 recent births in New York state found reductions in birthweights from 61 to 87 g depending on the level of maternal lead, 0 vs. 5, and 6 vs. 10 mg/dL, respectively.[165] Results from this extremely large study remind us that the inconsistencies in findings of pollutants and growth often can be explained simply by differences in the exposures of the populations studied.

Studies of birth weight are facilitated by routine collection of birth weight as part of public health surveillance. Studies of postnatal growth are less common. The largest studies have used national survey data from the US. Data from the second National Health and Nutrition Examination survey data (1976–80) involving about 7000 children less than 7 years of age showed that lead level was negatively related to stature, weight and chest circumference after controlling for other important influences on growth.[166] Compared to children with a blood lead level of zero, heights of children with the mean lead level were 1.5% shorter at the mean age of 59 months. The second large study used a data set of 7–12 year old children from the Hispanic Health and Nutrition Examination Survey (1982–84). Children whose blood lead levels were above the median for their age and sex, were 1.2 cm shorter than those with lead below the median.[167] The third study used anthropometric data from the Third National Health and Nutrition Examination Survey (1988–94) for non-Hispanic children 1–7 years of age, and found statistically significant reductions of 1.57 cm in stature and 0.52 cm in head circumference for each 10 μg of lead in the blood.[168] An analysis of 8–18 year old girls in the Third NHANES found that those with moderately high lead levels were significantly shorter.

Studies with smaller samples have also found growth decrements in height, weight and or head circumference of similar magnitude indicating that the associations of growth and lead reported for national samples of US children may be present generally.[169–171] Other anthropometric dimensions may also be decreased.[172] When lead levels are reduced in a neighborhood through public health efforts, child growth may respond positively[170] which suggests that early growth decrements may be reduced if the exposure is reduced early in life.

Many of these studies are cross-sectional, that is, lead and stature were measured simultaneously, and consequently one could argue (and some have) that short children are simply exposed to more lead. However, experimental studies with non-human animals show very clearly that growth is reduced following lead exposure, which supports the theory that lead is a cause of less growth.

Two longitudinal studies have reported that higher maternal blood lead levels coupled with higher infant lead levels was associated with poorer growth.[2,173] Reduced infant weight gain in relation to lead has been found in other studies as well.[174] Not all studies agree

and this may be attributed to differences in methods or/and levels of exposure or control for normal sources of variation such as diet, cigarette smoking, etc.

Several large studies with good measurement methods and control of relevant confounders have established quite clearly that lead exposure is related to delayed menarche and delay in attainment of Tanner stages.[175–180] Among African American girls in the NHANES III study, lead-associated delays in reaching Tanner stages ranged from 2 to 6 months depending on the Tanner stage, and menarche was delayed by 3 months.[176] A study of 10–16.9 year old girls found delays in reaching menarche of 10 months if their lead level was above the sample median compared to the average for those below the median.[2,178] Pubertal onset in Russian boys was delayed by some 6–10 months in boys.[177] Some dietary elements may moderate lead's effects on growth.[179,181]

A mechanism for the effect of lead on sexual maturation is suggested by the finding that girls in the Third NHANES sample with higher lead levels had lower levels of inhibin B, a marker of follicular development. Chelation therapy is applied to reduce high levels of lead in individuals. When children's lead levels are reduced, their stimulated peak human growth hormone levels are significantly higher compared to when lead levels are at a toxic level. In addition, among children with high levels of lead, IGF-1 is reduced with increasing lead level.[182] These results help make the statistical associations between lead and reduced height growth more understandable as true biological effects.

Over the past half dozen years, more and more studies have shown relationships between lead levels and growth and maturation. Moreover, the effects are seen at quite low levels that would have been of little concern 50 years ago. This fact reinforces the idea that growth is sensitive to environmental inputs, including or especially anthropogenic ones, and at relatively low levels and through day to day, chronic exposures.

Radiation

High doses of radiation, as are used for some cancer treatments, do affect height growth.[183] In these studies, the radiation dose is both high and carefully measured, and the effect on growth is well established. Everyday exposure to radiation is far harder to measure. Individuals have difficulty recalling all their exposures to mundane sources (i.e., medical X-rays, airplane flights) thus introducing error in measuring exposure. One study did find that women who had been exposed prenatally to medical X-rays were about 1.5 times more likely to experience menarche before the age of 10 years,[184] and others have detected postnatal growth retardation.

Studies of persons exposed through atomic bomb blasts have found that in utero exposure is associated with reduced head circumference, height and weight during childhood and adolescence and that the reduction is related to estimated dose.[185] One study of accidental

exposure to a bomb test found that early postnatal exposure is detrimental as well.[186] The most recent work on growth and radiation examined growth among survivors of Hiroshima and Nagasaki atomic bombs.[187] From 10 to 18 years of age, total in utero exposure was related to a reduction of several centimeters in stature, but it was not possible to see whether exposure in a particular trimester was especially damaging.

Microwave radiation is quite different from radiation from bomb blasts or cancer treatment, but is commonly experienced through mobile phone use. The growth of children and adolescents using mobile phones has not been studied, as yet, but reports of increased sleep disturbance related to greater phone use point to a possible indirect effect on growth.[188]

Stress

Stress is the body's reaction to a stimulus, termed a stressor, such as a threat of physical harm or an intense thought of that harm. A stress reaction to such stressors is labeled psychosocial stress. The stress response involves the autonomic nervous system and the endocrine system, and therefore intersects with the body's growth control mechanisms. Numerous observations of growth inhibition or delay testify to the connection between emotion and physical growth. Studies of infants who for no apparent reason (no underlying organic disease) fail to grow have shown that emotional turmoil in the environment can have a negative effect on growth. When such infants enter a socially and emotionally positive environment, their growth improves dramatically. This condition goes by many terms, failure to thrive, deprivation dwarfism and idiopathic growth failure.

A similar phenomenon has been described for older children as well. A classic study intended to determine the benefit of moderate nutritional supplementation provided to German children in orphanages after WWII found that emotional turmoil and psychosocial stress overpowered the effect of the supplementation.[189] Children in one orphanage who were not supplemented actually grew faster than those in the other orphanage who were supplemented but who were managed by a tyrannical and emotionally abusive headmistress. The childhood experience of anxiety disorders (diagnosed separation anxiety, or over-anxiousness) was associated with shorter stature in adult women and the presence of an anxiety disorder accounted for 5% of the variance in adult height; no relationship was observed in males.[190]

In cases of extreme deprivation or stress the growth inhibition can be substantial. Children adopted in the US from institutions in foreign countries tend to be small for age and delayed in growth and maturation. An extreme case of social and emotional deprivation was experienced by Romanian children who had been abandoned by the parents and were warehoused in orphanages during the Ceaușescu communist era. When the Ceaușescu

regime ended and the children were studied, their growth was much affected by their confinement and their emotional and social deprivation.[191] Fig. 10.4 shows just how small the boys were. From age 6 through 18, they averaged approximately 3.5 standard deviations below US (CDC) reference values for height and weight which is equivalent less than the first percentile. Girls were equally small for their age. Sexual maturation of both sexes was delayed by 1.25−2.75 years, equivalent to several z-scores lower compared to reference children. These findings of delayed sexual maturation contrast with those studies that find earlier sexual maturation in girls following sexual abuse or from father absent households (see chapter 5) which can be considered another form of psychosocial stress.

The difference in findings tells us that other variables must be involved to account for the variation in results. These variables are likely to be the stage of development when the stressor is experienced, and the type of stress. Both could be important in producing the resulting change in growth and development and need further study.

Some stressors are not from the social environment but from physical sources and they stimulate the stress response also. Noise, defined as unwanted sound, is a classic physiologic stressor used in countless lab studies to induce stress responses in experimental animals. In some ways, noise is easier to measure than psycho-social stimuli and the growth response more accessible to study.

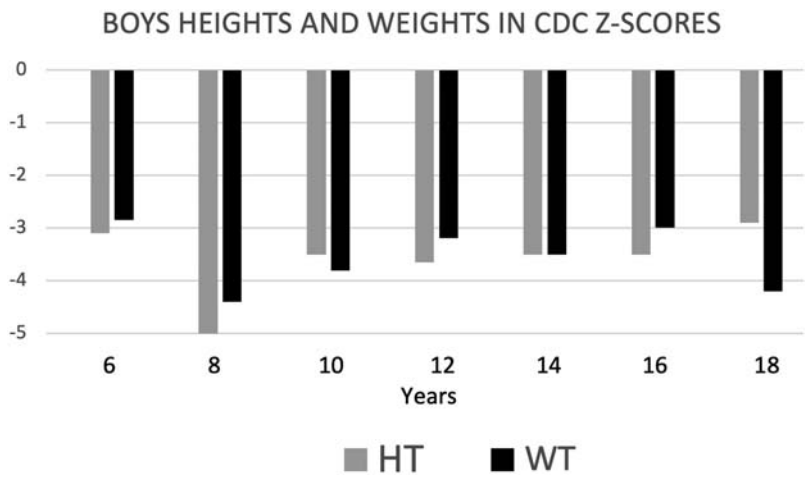

Fig. 10.4

Romanian orphanage boys' height and weight z-scores, all negative indicating smaller size than CDC means for age. *Source: Adapted from Himes J.H., Park K., Iverson S.L., Mason P., Federici R., Johnson D.E., Physical growth and sexual maturation of severely deprived children reared in Romanian orphanages. In: Ashizawa K., Cameron N., Human Growth in a Changing Lifestyle Smith-Gordon London, 2009, 79−84.*

Several studies have examined prenatal growth in relation to maternal exposure to stressful noise from the workplace and have found small effects on birthweight or, in one case none at all.[192,193] Road traffic noise is different because it occurs during the day and night as well as during mealtimes when people find it most annoying and stressful. A metanalysis using over 700,000 birth records found birth weights reduced by 8 g in relation to road traffic noise.[194] Noise stress is more severe near airports and noise exposure may be more accurately measured compared to traffic noise studies. The percentage of low birth weight births doubles or nearly doubles in several studies of circum-airport samples.[195–200] Two studies have found similarly sized reductions in birth weight or increases in low birth weight related to aircraft noise and both studies found these effects among female births but not males.[197,200] Other studies have not examined effects by gender, but further research might determine whether effects of stress on growth differ by gender.

Evidence for an environmental effect on growth depends on different lines of evidence (see Table 10.1) and these are present among the studies of noise stress. There is evidence of a dose response relationship (see Fig. 10.5).[199] The temporal relationship was established in a study of birthweights near Kobe airport in Japan. Prior to the introduction of jets, the rate of low birth weight was lower near the airport compared to the rest of Japan, but as soon as jet flights began, the rate of low birth weight increased markedly and the increase continued to parallel the increased number of jet take-offs. The temporal association strongly suggests that the jet take-offs are causally related to the change in the frequency of low birth weight. True experimental studies of animals demonstrate effects of

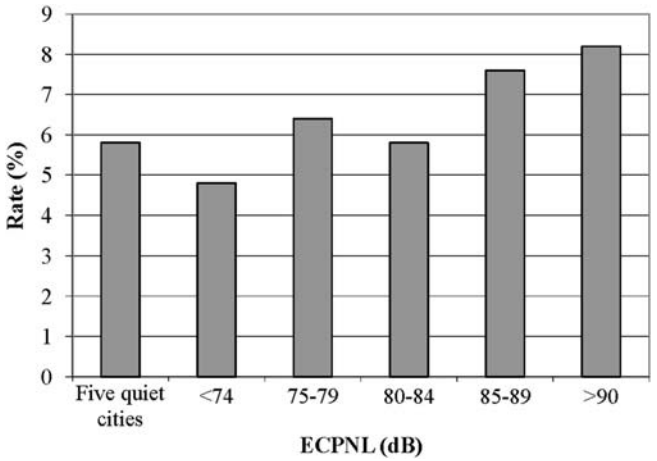

Fig. 10.5

Percentage of low birth weight infants (<2500 g) in 1969 according to mothers' exposure to aircraft noise measured as Equivalent Continuous Perceived Noise Levels (ECPNL) (dB). *Source: Adapted from Ando Y, Hattori H. Statistical studies on the effects of intense noise during human fetal life.* J Sound Vib. *1973;27(1):101–110.*

noise exposure on prenatal and postnatal growth. The biological plausibility of the statistical associations seen in studies of humans is strongly supported by the animal studies.

Studies of postnatal growth are very few perhaps owing to the difficulty of estimating noise exposure for postnatal life. The first such study found reduced heights and weights among the children exposed to high noise from an airport in Japan. Later studies have found a reduction in height at 3 years of age (see Fig. 10.6) and a reduction in soft-tissue dimensions in children 5–12 years of age.[163,201] Some recent studies have found increased frequency of overweight in relation to prenatal and postnatal noise exposures.[202,203]

An effect of noise seems plausible based on what we know about the relationship of high noise to the stress response and the relationship between stress and growth. Noise activates the hypothalamic-pituitary-adrenal axis in the same way that other stressors do (see Fig. 10.7). Noise stress stimulates the autonomic nervous system and the pituitary gland which in turn affects the adrenal cortex, the thyroid and the gonads. Support for this causal chain comes from a study in which cortisol was elevated in adolescents in relation to annoyance from road traffic noise; annoyance is an indicator of stress.[204] Cortisol, thyroid hormones and sex steroids all affect growth and development. Thus, an effect of noise on

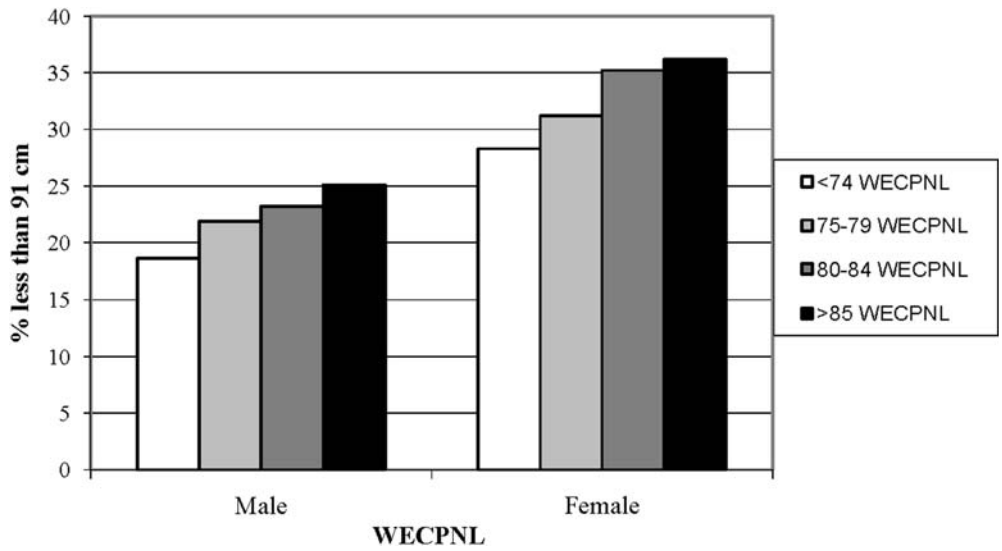

Fig. 10.6

Percentage of 3-year-old children <91 cm tall by noise exposure measurement Weighted Equivalent Continuous Perceived Noise levels (WECPNL). *Source: Adapted from Schell LM, Ando Y. Postnatal growth of children in relation to noise from Osaka International Airport.* J Sound Vib. *1991;151(3):371–382.*

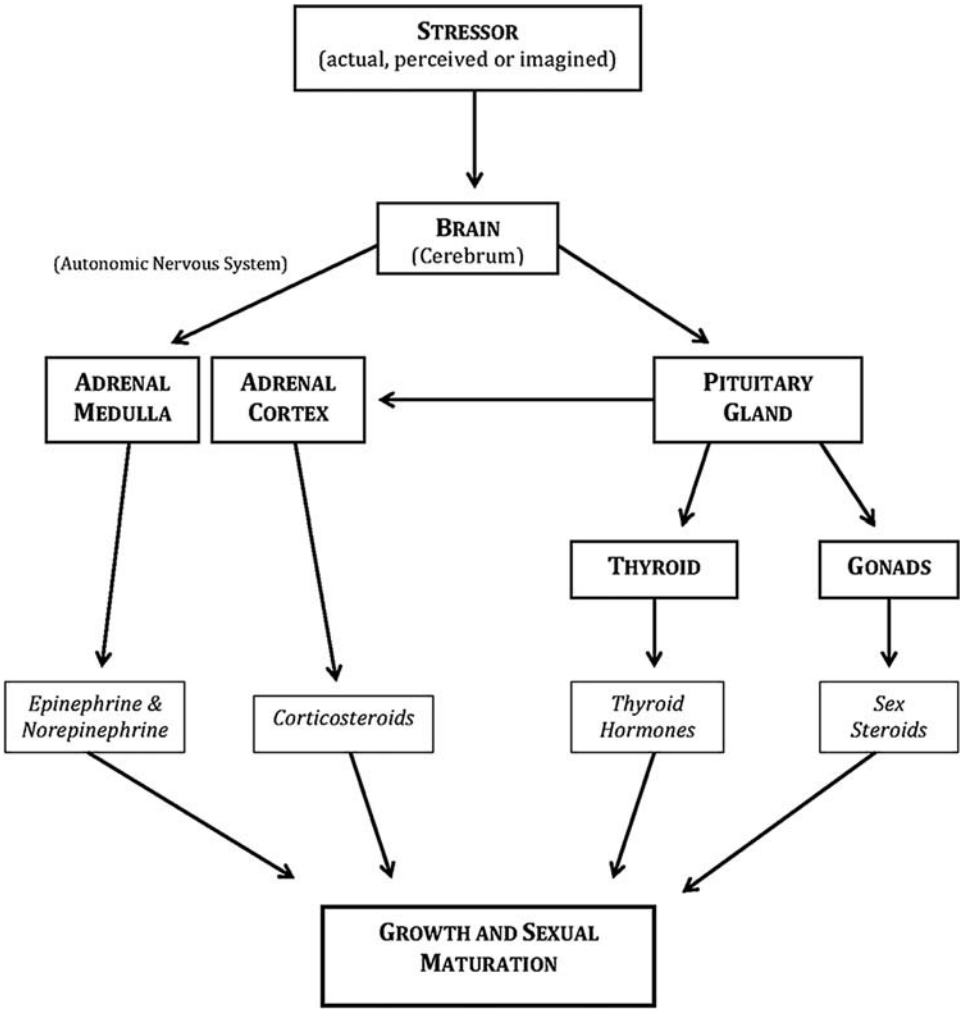

Fig. 10.7
The biological stress response.

growth is biologically plausible. Since noise is a form of stress, studying noise exposure is a way of learning about the effects of other kinds of stress as well.

One general observation is that the effects of any pollutant depend on the dose. Effects of noise are not present in any study unless the exposures are quite high, perhaps over 100 dBA. Statements summarizing the relationship between noise and growth have to be careful about specifying the range of exposure observed. In general, statements about the relationship between any environmental factor, whether it is altitude or noise, should refer only to the ranges of exposures observed and should not extrapolate results to exposures

above or below that range of the observations, otherwise results among studies will appear more inconsistent than they really are.

Social and economic influences on postnatal human growth

Disparities in human growth are a persistent feature in human society with much of the observed variation attributable to the social and economic conditions of individuals, households and communities. Disparities in growth begin in the prenatal period and continue through infancy, childhood and adolescence resulting in differentials in adult stature and body composition. The magnitude of these differences in growth reflects the extent of socio-economic inequality, as highlighted by Tanner's "*growth as a mirror of the condition of society*".[205] In low-resource environments, or disadvantaged communities, impaired linear growth is an important indicator of the extent of environmental insult. More specifically, stunting prevalence (height-for-age below -2 standard deviations of the WHO reference or standards) across the life course is a common benchmark for assessing impairments in linear growth at a global scale.[206]

The UNICEF conceptual framework,[207,208] developed originally to identify determinants of undernutrition, can be adapted to provide a contextual approach to understand how adverse social and economic conditions impact on growth primarily applied to low and middle-income country settings.[208,209] The framework identifies the *immediate causes* of poor growth as disease and inadequate dietary intake in these contexts. These immediate causes are directly influenced by the household environment (*underlying causes*) including household food security; maternal education and child care, and household access to water, sanitation and health services. Beyond the household environment, the higher level of *basic causes* of impaired growth include economic and socio-political structures and policies. These, in turn, determine human, financial, physical, social and natural capital (Fig. 10.8).

Human growth studies have variously examined the environmental effects on growth at the individual, household and wider socio-political structural levels. These layers of proximal and distal determinants of growth will be reviewed in the following sections with an emphasis on populations that experience the most disadvantaged environments and greatest deficits in growth.

Immediate causes: infection and nutrition

The nutritional determinants of human growth and development are covered in Chapter 7, hence this section will focus on the other immediate cause of poor postnatal growth: infection. Episodes of illness and infectious diseases contribute to short term reductions in

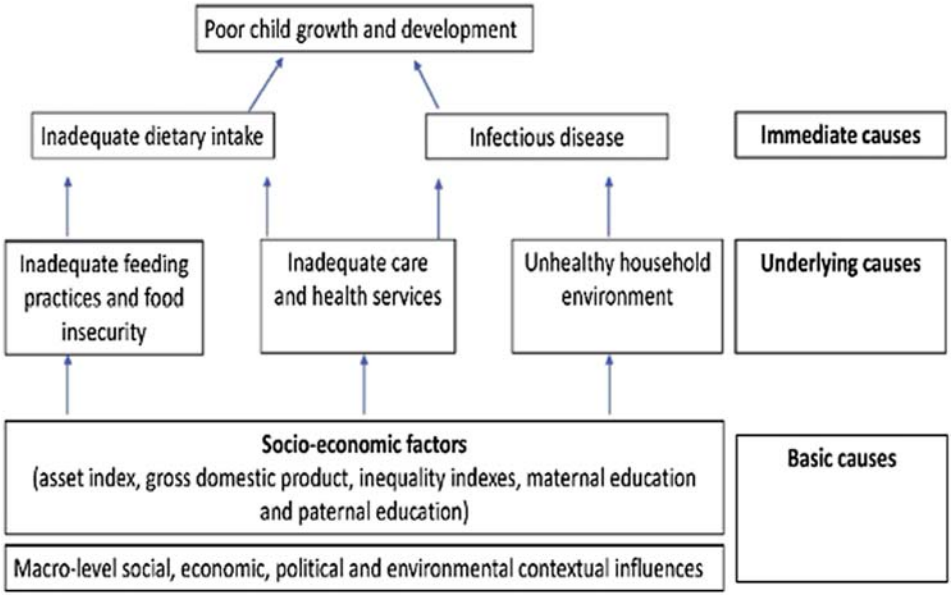

Fig. 10.8

Conceptual framework of the immediate, underlying and basic causes of poor growth. *Adapted from UNICEF Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences. Lancet. 2008;371(9608): 243-260; United Nations Children's Fund. UNICEF's Approach to Scaling up Nutrition for Mothers and their Children. Discussion paper. New York; 2015; Huicho L, Vidal-Cárdenas E, Akseer N, et al. Drivers of stunting reduction in Peru: a country case study Am J Clin Nutr. 14;2020;112(2):816S-829S.*

weight gain and linear growth,[208,211] and repeated episodes can lead to long-term growth faltering and shorter adult stature. Infectious diseases are therefore an important determinant of poor growth in children under 5 years of age.[208] The most common infectious diseases contributing to adverse growth in childhood are malaria, respiratory infections, and diarrheal diseases. Assessing child morbidity from infectious diseases in young children is rarely possible from routinely collected data due to biases in attendance at health centers, variable quality of record keeping and the unknown extent of unreported illness. Household surveys, however, have shown that self-report or maternal recall of infectious diseases of their children are significantly associated with growth. In Bangladesh, maternal reports of child illness were significantly associated with monthly changes in weight-for-age, and mid-upper arm circumference (MUAC) of young children (aged 2−6 years). The greatest reduction in weight gain was associated with reported episodes of fever, followed by episodes of diarrhea and respiratory infection.[21] Similarly, these reported episodes of illness were associated with markers of inflammation and acute phase proteins,[22] showing that these reported symptoms corresponded with biochemical changes in the immune response.

Of the common infectious diseases, diarrheal diseases play a particularly important role in growth retardation in infants and young children.[208] Analysis of longitudinal child growth data from Bangladesh, Brazil, Guinea-Bissau, Ghana and Peru showed that risk of stunting increased multiplicatively with each episode of diarrhea in the first 24 months of life.[208] A detailed analysis of multi-site data from four countries (Brazil, Peru, Guinea-Bissau and Bangladesh) found that diarrheal episodes were associated with slower linear and ponderal growth in a 3 or 6-month period, but catch-up growth in length occurred in the 3 months after an episode of diarrhea.[212] The reality in many low resource contexts, however, is that infants and young children experience repeated episodes of diarrhea, with limited "disease-free" periods as opportunity for catch-up growth, hence the resultant long-term growth deficits.

Children living in poverty and socio-economic disadvantage are likely to have both a higher incidence of diarrheal diseases, and greater severity of disease. In the MAL-ED study, a large birth cohort from eight countries, mothers of children with subclinical enteric infections caused by the bacteria *Escherichia coli* (See Box 10.1) were more likely to be coinfected with other enteric pathogens, and these mothers also had lower levels of education, poorer hygiene and sanitation, lower socioeconomic status, and lower breast-feeding rates compared to mothers of children in whom no pathogen was detected ($P < 0.05$).[213]

The mechanisms by which diarrheal diseases cause impaired growth during infancy and childhood are still a subject of investigation. Contributing factors include malabsorption of nutrients, reduced appetite and, over a sustained period, the condition known as environmental enteric dysfunction (EED). EED is understood as an acquired subclinical disorder characterized by damage to the lining of the small intestine including shorter or blunted villi, the finger-like structures for nutrient absorption, and longer crypts (the grooves situated between villi in the mucosal epithelium). This damage to the gut is observed in early life in low resource settings and is thought to result from exposure to fecal contamination of the environment and infection with gastrointestinal pathogens.[214] Research in this field is hampered by difficulties in assessing the integrity of the small intestine, other than by gut biopsy which is ethically and technically unfeasible in the environments where this is prevalent.[214] However, various biochemical indicators of inflammation (e.g. alpha-1- acid glycoprotein, C-reactive protein, ferritin and immunoglobulins (IgG, IgM)) are associated with both impaired growth and diarrheal disease. Other potential tests indicating damage to the gut mucosa include intestinal permeability which assesses the absorption of a controlled dose of sugars (lactulose and mannitol) from the gut via urine sample analysis, or fecal calprotectin, a protein released by neutrophils. While there is considerable evidence that the health of the human intestinal tract plays an important role in sustaining normal growth, the exact pathways linking microbial exposure, intestinal damage and impaired linear growth are still debated.[214]

Box 10.1 Household environmental contamination: a case study of *E. coli*.

E. coli (*Escherichia coli*) is a common bacterium found in water, food and the natural environment such as soil and surface waters (e.g. rivers, ponds and canals). It is also a commensal organism of the human and animal gut and is shed via feces. The presence of non-pathogenic *E. coli* in the physical environment is commonly used as an indicator of fecal contamination. In this way it can be used as a proxy indicator of the environmental risk of diarrheal disease or faecal-oral pathogens. Soil is an excellent reservoir for pathogenic and commensal bacteria such as *E. coli*, and rural households in many contexts rely on compacted mud floors internally and in courtyards or "backyards". Fecal contamination in these environments arises not only from human sources, but also from livestock and animals sharing the same household environments. In rural communities, poultry commonly roam freely in kitchens or household compounds in the same areas where young children sit, crawl and play. Even in urban areas, mud floors are common and domestic animals live in close confines with humans.[215] Other forms of fecal contamination within the home arise from the use of animal manure in compound floors and walls and as household cooking fuel. Finally, the provision of clean water at source does not always equate with clean water being used in the home. Other environmental sources of *E. coli* bacteria include drinking water, particularly storage containers, food and other household utensils.

A study in Bangladesh examined fecal contamination pathways by analyzing the number of *E. coli* bacteria in samples from human hands, household floors, food, stored water and flies, in relation to the number of *E. coli* in the "natural" environment (soil, ponds) and domestic animals.[216] For each increase in the environmental contamination (soil and ponds) there were significant increases in the level of contamination on hands, food and stored water. Domestic animals were also a significant contributor to contamination. The study was conducted in households that had already received improved sanitation, demonstrating that multiple pathways of fecal contamination exist even in improved environmental conditions.[216]

As well as commensal *E. coli*, there are pathogenic forms of *E. coli* that cause enteric (intestinal) infection and other forms of infection such as urinary tract infections. There are five disease-causing forms of enteric *E. coli* namely: enterotoxigenic *E. coli*; Shiga toxin-producing *E. coli*; enteroinvasive *E. coli;* enteropathogenic *E. coli* and enteroaggregative *E. coli* (EAEC).

Long-term, chronic infections, such as intestinal parasites, are further candidates for impaired growth of children and adolescents through reducing the absorption of dietary nutrients, as well as immune inflammation and anemia. Among the most common intestinal parasites are soil-transmitted helminths (roundworm, hookworm and whipworm) and schistosomiasis. Despite the widespread prevalence and high transmission of these parasites, it has proven difficult to quantify the effect of these infections on child growth.

Treatment for intestinal parasites is affordable, safe and readily administered, and regular (annual or biannual) deworming for soil-transmitted helminths has been recommended by the World Health Organization for pre-school and school-age children where the prevalence of these infections is 20% or higher.[217] However, large-scale trials to evaluate the impact of mass deworming on child growth have shown inconsistent results, with small to non-significant effects on growth.[218] Explanations for these inconsistent results include the relatively low intensity of infections (low number of parasitic worms) in most of the affected populations; the rapid rate of reinfection, and, as with other examples of interventions in this section, the difficulties of bringing about measurable improvements in child growth through controlled intervention trials.

What we can infer from the epidemiological evidence on child growth and infectious disease is that there are clear disruptions to growth during periods of illness, and the more repeated episodes of illness, the greater the physical impact on growth. However, targeting a single infectious disease or parasitic infection may not, in isolation, have a measurable impact on growth without improvements in the wider environmental and social determinants of growth.

Underlying causes: household water, sanitation, hygiene and growth

Observational, cross-sectional and longitudinal studies provide strong evidence of the association between physical environments at the household level and child growth. For example, in Colombia, access to sanitation was significantly associated with a lower prevalence of stunting for children and adolescents.[219] It is far more challenging, however, to generate evidence demonstrating that ameliorations in the physical environment can lead to significant improvements in child growth.

Three recent large-scale, cluster-randomized trials aiming to improve growth from birth to 24 months of age through water, sanitation and hygiene (WASH) interventions have shed important light on this topic.[220–222] In contrast to previous interventions focusing on a single determinant of growth (e.g. disease reduction or nutritional supplementation) these trials addressed both the immediate and the underlying causes of poor growth. The "WASH Benefits" trials took place in rural Kenya and Bangladesh including trial arms with nutritional counseling and supplementation (a lipid-based nutrient supplement providing energy, vitamins and minerals) as well as WASH interventions (single and combined intervention arms for clean household water supply, improved sanitation and behavior change communication programmes to promote handwashing with soap).[220,221] Despite high adherence and retention to the interventions, the impacts on child growth were less significant than anticipated. In Bangladesh, diarrhea prevalence was reduced in the intervention group, but combined water, sanitation and handwashing interventions provided

no significant improvements in linear growth after a 2-year intervention.[220] In Kenya, diarrheal disease was not significantly reduced in children, but there were small improvements in growth in the group receiving nutritional supplements and counseling in addition to water, sanitation and hygiene interventions. However, the nutrition interventions alone provided the same degree of growth improvement as the combined nutrition plus WASH arms.[221] Hence, there was no evident benefit of WASH interventions. The third intervention study, the SHINE trial took place in Zimbabwe.[222] As with the previous trials, the interventions led to improvements in infant and young child feeding practices, but the WASH components had no impact on linear growth.[222] Explanations of these limited improvements in growth following high quality environmental interventions have highlighted the residual high level of disease burden in these communities. Even after receiving WASH interventions, children had high exposure to enteric infections, up to ten times greater than children in high income settings.[215] Recommendations have been made to reduce fecal contamination of the environment radically through rigorous evaluation of the effectiveness of improvements to water, sanitation and hygiene in the home environment.[215]

Basic causes: poverty, socio-economic status and parental education

Multiple indicators of socio-economic status (SES) or socio-economic position (SEP) exist. Studies range from the use of one indicator, such as household wealth or income, to composite indicators such as a "wealth index" based on a combination of education, occupation, income, material goods and assets, or consumer durables. Regardless of which indicators are used, lower socio-economic status is consistently associated with reduced linear growth and height. Mansukoski et al.[223] analyzed anthropometric data from successive cohorts of school children aged 3–19 years in Guatemala city, Guatemala, between 1955 and 1993. Children were classified into five socio-economic position (SEP) groups based primarily on the type of school attended (private vs. state and level of fees) as well as parental occupation and education. Across all cohorts during the period of study, the mean prevalence of stunting was 2.9% in children from the highest SEP group compared to 52% in the lowest SEP group.[223] This study also illustrates the minimal growth deficits among higher socio-economic groups, even when the national prevalence of stunting or underweight may be high. In India, anthropometric indicators (height-for-age, weight-for-age and weight-for-height) of healthy young children aged 12–23 months from the highest socio-economic group were close to the median NCHS/WHO reference population.[224]

Large, cross-sectional studies have demonstrated the independent effects of multiple factors associated with socio-economic status. In Pakistan, for example, significant correlates of stunting in children aged 5–12 years were: living in a rural area; living in an

urban area with low socio-economic status; a low-income neighborhood; lower parental education, more siblings, crowded housing and cigarette smoking in the household.[225]

Socio-economic influences on growth in weight are more complex, with many populations displaying a transition as the host country moves through stages of economic development. In the early stages of economic transition to urbanized, industrialized societies, the prevalence of overweight and obesity increase initially among the higher socio-economic sectors. As a country's gross national product increases, however, overweight and obesity prevalence tends to shift toward the lower socio-economic groups.[226] In many populations worldwide, there is now a double burden among lower socio-economic groups which experience reduced linear growth accompanied by rapid weight gain in childhood and adolescence, leading to increased risk of overweight and obesity.[206] Among the Birth to Twenty birth cohort in South Africa, at the early stages of nutrition transition, body mass index and fat mass in 9−10-year olds were higher among the higher tertile SES group (based on employment and material goods ownership) compared to the lower SES group.[227] Similarly, in other middle-income countries these converse associations between stunting and obesity prevalence across socio-economic groups are apparent. In Colombia, national survey data showed children and adolescents from the poorest households were almost five times more likely to be stunted, while those from the richest households were approximately twice as likely to be overweight than their poorer counterparts.[219]

Examination of growth patterns and the nutrition transition has also shown that the shift of obesity toward lower socio-economic groups occurs in women at an earlier stage of the transition compared to men.[226] The South African Birth to Twenty cohort data from adults aged 19−20 showed sex differences in the association between socio-economic status and body composition.[228] In men, a low or middle household wealth index was associated with a higher prevalence of low BMI ("thinness"). Among women in the same environment, however, a low household wealth index was associated with lower odds of being thin and greater propensity for overweight or obesity.[228]

Sub-optimal growth is more common among children of mothers with a lower level of education. In low and middle-income country contexts this is likely to result in a higher prevalence of stunting.[209,229] The mechanisms underlying the association between parental education and growth are multi-faceted. In some cases, specific child care behaviors have been shown to vary significantly by parental education. For example, in Bangladesh and Indonesia, higher levels of parental education were associated with protective behaviors such as use of a closed latrine, use of the local health center, and uptake of interventions such as vitamin A supplements, iodized salt and child immunisation.[230] These factors may not all be directly associated with growth *per se*, rather, they are likely to reflect the general

ability of parents with higher educational attainment to implement child care practices and behaviors that promote growth. In Columbia, demographic and health data from children and adolescents showed that care practices and household characteristics, including mother's education, explained over one-third of socio-economic inequalities in stunting.[219]

Distal determinants: structural, economic and socio-political environments

Rapid improvements in growth of children, as indicated by reductions in stunting prevalence, have been observed at a national level in several countries in recent decades. In some cases, these improvements have been achieved through multi-sectoral programming, policy and targeted interventions, as in the case in Peru[231](See Box 10.2). In other cases, improvements have come about without interventions directly targeting growth, but instead through the distal determinants that include changes in the broader socio-political and economic environment. These, in turn, have led to reductions in poverty, improved education or other underlying/proximate causes. Economic development in Brazil was accompanied by policies for income and basic service redistribution.[229] During this time stunting prevalence declined from 37.1% to 7.1% from 1974/5 to 2006/7, with the greatest reductions in the poorest quintile (59.0%−11.2% stunting prevalence) compared with the wealthiest quintile (12.1%−3.3%). The poorest groups showed the greatest improvements in family purchasing power, maternal education, access to healthcare and to water and sanitation services.[229]

Milman et al.[232] examined the role of distal (basic) and proximal (underlying) factors on stunting across 85 low-income and middle-income countries that had national survey data taken at least 4 years apart. The data were modeled to examine which factors were associated with reductions in stunting and reported that both developmental indicators (basic or distal determinants) including income distribution, government consumption and the proportion of the economy devoted to agriculture and specific interventions including immunization rates, access to safe drinking water and female literacy were independently associated with improvements in stunting.[232]

In Cambodia, rapid economic growth and peace during the 2000s was associated with a reduction of child stunting in under 5-year olds from 49.3% in 2000 to 39.0% in 2010.[233] Analysis of national survey data demonstrated this economic growth was associated with changes in underlying factors: household wealth was the greatest contributor to stunting reduction, followed by improvements in sanitation facilities, parental education, birth spacing and a decrease in maternal tobacco use.[233]

Box 10.2 Interventions to address economic and socio-political determinants of stunting: a case study from Peru.

Peru is a middle-income country. Following a period of political instability, dictatorships and guerrilla warfare in the 1980s and 1990s, the country achieved greater political stability and rapid economic growth. At the beginning of the 2000s, the prevalence of stunting reflected the marked inequalities in socio-economic status, rural-urban residence and regional disadvantages, with particularly high rates of stunting in rural populations in the Amazon and Andean regions. However, Peru achieved remarkable success by halving the prevalence of stunting in children under 5 years from 30% in 2007 to 13.1% by 2016.[210,231] Most recent national data show the national stunting prevalence declined further to 12.2% for under 5s.[234]

These dramatic reductions in stunting came about through concerted efforts across all government departments and multi-sectoral approaches to tackle poverty and disadvantage, evidenced by the proportion of the population living below the poverty line which fell from 47·8% to 23·9% from 2007 to 2013 alongside the reduction in stunting.

As well as many health, social and food policy initiatives across government departments, conditional cash transfer schemes were also employed in 2005. The condition of the cash transfer scheme, known as the JUNTOS, was that recipients had to attend maternal and child health services and education, hence poor households received cash through adherence to the conditions such as school attendance, childhood vaccinations and growth monitoring appointments.[231] This scheme also had the specific aim of breaking the intergenerational cycle of poverty and poor growth. Regional populations with particularly high stunting prevalence and poor health outcomes were identified in the Andean and Amazon regions. These groups were then targeted for the JUNTOS conditional cash transfers and the government health insurance program.[231]

Further innovations of this scheme included rolling out interventions to the poorest sectors of society first before any other groups. For example, new vaccines (*H. influenzae* type B, pneumococcal, and rotavirus) were administered first in the poorest regions of the country, as a further step to reduce inequalities in a short time period.[231]

In sum, this case study shows how the Peruvian government used all three levels of the conceptual framework to reduce stunting. The multisectoral government programmes and targeted pro-poor interventions came about through political will, economic growth and societal participation. This was accompanied by a significant increase in financial expenditure on health and other sectors to achieve the intended outcomes.

Future actions to tackle adverse growth environments

Global actions to improve growth have been developed with a specific target of a 40% reduction of the number of children under 5 years who are stunted by 2025.[206] The

proposed areas of activity to reduce stunting include: tackling the double burden of malnutrition (the coexistence of undernutrition and stunting along with overweight and obesity, see below); addressing health inequalities; improving access to clean water, proper sanitation and management of solid water; social protection polices, and actions to support agriculture, food systems under the threat of climate change. Individual level factors also include nutrition education; prevention of early marriage; promoting completion of secondary education; improving socioeconomic status and control over resources, and improving access to water, sanitation and cooking-fuel facilities.[206]

As the nutrition transition progresses in low- and middle-income countries, policy makers can no longer focus efforts to improve the environment on linear growth deficits or stunting alone. Instead, policies need to consider multiple forms of malnutrition that occur within the same population. In some cases, this may be the dual challenge of impaired linear growth alongside excess weight gain among children, adolescents and adults. In other examples the multiple forms of malnutrition might include anemia, stunting and overweight or obesity. With this in mind, the WHO has proposed policy actions to address the double burden of malnutrition, through "double duty" actions for governments to incorporate into nutrition and food policies.[235] Growth deficits due to undernutrition and excess adiposity due to overnutrition can both be tackled through such integrated policies. These are known as the WHO Double Duty actions. Actions include the promotion of individual behaviors such as promotion of exclusive breastfeeding to optimize early nutrition, maternal nutrition and antenatal care programmes, as well as national level school food policies and programmes, and marketing legislation.[235]

Finally, addressing environmental determinants of impaired growth can be seen as an integral component of the United Nations Sustainable Development Goals.[236] While many of the 17 Goals bear relevance to human growth and development through the close interconnectedness of the physical, social and natural environments, the first six goals are of relevance to the factors that have been explored in this section. Namely: Sustainable Development Goal (SDG) 1, No poverty; SDG2, Zero hunger; SDG3, Good health and wellbeing; SDG4, Quality education; SDG5, Gender equality and SDG6, Clean water and sanitation. Progress toward meeting these goals by 2030 should lead to significant improvements in human growth and development worldwide.

How do we interpret differences in growth related to environmental factors?

Recalling the two interpretations of growth reductions reviewed at the chapter's outset, it seems that the interpretation used depends on the environmental factor considered: slow and/or reduced growth is a disadvantage created by adverse health conditions (this is the

growth monitoring or "biomedical" model), or slow and/or reduced growth is an adaptive response (i.e., beneficial) to features of the environment (the adaptation model). While there is no covering law to dictate which interpretation is appropriate in which circumstances, in general it seems that growth reductions related to anthropogenic factors (lack of material resources for the child including poor medical care and poor nutrition) tend to be interpreted with the growth as a monitor model while growth reductions related to long-standing features of the physical environment (e.g. temperature, altitude) tend to be interpreted in an adaptive framework. This distinction is not foolproof. Air pollution, an anthropogenic factor, is also a product of volcanoes and other natural processes. Ultimately the view that growth reductions do have adaptive benefits for the individual (affecting reproduction, or functioning such as cognition performance) will be determined by studies that seek to measure the adaptive benefits. In general, growth alterations may be seen as the result of trade-offs between resources for growth, reproduction or survival.

Conclusion

In addition to effects of nutrition and social-economic factors, the immediate physical environment can affect human physical growth and development. This conclusion is supported by many of the studies reviewed here on altitude, temperature and climate. Studies of pollutants also show effects on growth, although many of these studies have flaws that come from valued and important limitations on experiments with people. However, the results from numerous, carefully executed studies of non-human animals support the studies on humans. When compared to the effect of malnutrition, the effect of pollutants can seem small, but the size of the effect depends on the extent of exposure to the pollutant. If we clean up the environment, child growth will be little affected by air pollution, but if children grow up in an environment with many types of pollution, the effect of all the pollutants together may be large. Indeed, studies show that in industrialized countries the poor children have more exposure to pollutants, and the result can be impaired growth. It is wise to remember that exposure to many of the pollutants that affect growth are mediated by social factors as is nutritional deprivation. Thus, growth can be considered as a monitor of the general quality of children's environments.

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Further reading and resources

For Information on Toxic Substances and Health: http://www.atsdr.cdc.gov/.
And for Information on Specific Toxicants go to: http://www.atsdr.cdc.gov/toxprofiles/index.asp.
For Information on Toxicants and the Environment Including some Information on Human Health Effects: http://www.epa.gov/.
For more Information About Noise Pollution: http://www.nonoise.org/.
For more Information About High Altitude: http://www.altitude.org.

For further reading and research.

High Altitude: For a review of adaptations to high altitude see Beall, Adaptation to high altitude: phenotypes and genotypes. *Annu Rev Anthropol*. 2014;43:251−72. 10.1146/annurev-anthro-102313-030000. Lampl outlines theoretical debates over prenatal growth in, Cellular life histories and bow tie biology. *Am J Human Biol*. 2005;17(1):66−80. doi.org/10.1002/ajhb.20094. The quarterly journal High Altitude Medicine and Biology, available online, offers periodic reviews of problems confronting high altitude populations or visitors.

Regarding pollution and growth: The journal, Environmental Health Perspectives is a good source on pollution and health. For a review of polychlorinated biphenyls and health see Carpenter DO. Polychlorinated biphenyls (PCBs): routes of exposure and effects on human health. *Rev Environ Health*. 2006; 21:1−23. For a recent review of pollution and human biology see any of these: Schell LM, Industrial pollutants and human evolution. In: Muehlenbein MP, eds. *Human Evolutionary Biology*. Cambridge: Cambridge University Press; 2011:566−580, or Schell LM, Burnitz KK, Lathrop PW. Pollution and human biology. *Ann Hum Biol*. 2011;37(3):347−366. Impact of pollution on physiological systems: taking science from the laboratory to the field. Schell LM. In: Mascie-Taylor N, Yasukouchi A, Ulijaszek S, eds. *Human Variation: From the laboratory to the Field*, London: Taylor and Francis:131−141. Series; vol. 48.
Socio-economic influences on growth.

Further reading

The Global Nutrition Report is published annually and provides up to date information on the status of nutrition. In The 2020 report, Chapter 2: Inequalities in the Global Burden of Malnutrition https://globalnutritionreport.org/reports/2020-global-nutrition-report/.

For further understanding of environmental enteric dysfunction and links with childhood growth read: Tickell KD, Atlas HE, Walson JL. Environmental enteric dysfunction: a review of potential mechanisms, consequences and management strategies *BMC Med*. 2019;17:181. https://doi.org/10.1186/s12916-019-1417-3.

For an example of the conceptual framework of child undernutrition in relation to socio-economic and structural determinants with reference to Peru see.

For further reading about The UNICEF Framework of childhood malnutrition Black RE, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet*. 2008;371(9608):243−260. https://doi.org/10.1016/S0140-6736(07)61690-0.

To read more on how the UNICEF framework has been applied to Peru see Huicho L, et al. Drivers of stunting reduction in Peru: a country case study. *Am J Clin Nutr*. 2020;112:816S−829S. https://doi.org/10.1093/ajcn/nqaa164.

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CHAPTER 11

The measurement of human growth

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Introduction

This chapter deals with measuring growth using anthropometric methods to assess the external dimensions of the body such as height, weight, and measures of subcutaneous fat. Chapter 19 deals with the assessment of body composition in relation to growth and some of the methods required to do this, e.g. measures of subcutaneous fat using skinfolds, will be covered in this chapter also. The anthropometric methods used to assess human growth have been described by me in a number of publications including in a book, "*The Measurement of Human Growth*"[1] and various book chapters and articles[2–5] which may be available in your university library. This "lecture" will necessarily borrow heavily from those publications to maintain the need for standardization of techniques and consistency of description.

Clearly it is vitally important that all those who assess human growth do so using similar methods so that their data are comparable between individuals in the same study and between samples in different studies. The universal standardization of anthropometric measurement has been a desire of those who measure the human body since the 19th century. However, the anthropometry peculiar to human growth that we use today had its most recent development in the American longitudinal studies of the first half of the 20th century. From 1904 to 1948, 17 such studies were started and 11 completed. Their complexity varied from the relatively simple study of height and weight to data yielding correlations between behavior, personality, social background and physical development.[1] Researchers were aware of the need for comparability of measurements and published precise accounts of their methods and techniques, with suitable adaptations for the measurement of growth. The three most important and informative accounts from this period are those of Frank Shuttleworth[6] for the Harvard Growth Study of 1922, Harold Stuart[7] for the Center for Research in Child Health and Development Study of 1930, and Katherine Simmons in her reports of the Brush Foundation's Studies of 1931.[8] In Britain, few longitudinal growth studies were undertaken before 1949. However, the Harpenden

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Longitudinal Growth Study, managed by J.M. Tanner and R.H. Whitehouse from 1949 to 1972, became the strongest influence on British studies of human growth and did much to advance the anthropometry applied to human growth (often referred to as "auxological anthropometry"). The team of Tanner and Whitehouse radically altered the approach to auxological anthropometry. Whitehouse, for example, was dissatisfied with the instrumentation available and developed the "Harpenden" range of instruments that eliminated graduated rules for measuring linear distances (e.g. height) in favor of counter mechanisms. These counters were turned by a simple ratchet system and displayed the measurement in millimetres which reduced reading errors.

The series of longitudinal growth studies co-ordinated through the International Children's Center in Paris between 1960 and 1980 had a major effect on standardizing anthropometric measurements and growth study design. Research teams from growth studies in Belgium, Britain, France, Senegal, Sweden, Switzerland, Uganda and the USA met every two years to initially discuss their methods and eventually their results which resulted directly or indirectly in a bibliography of 948 references.[9] The International Biological Project from 1962 to 1972 brought together scientists from all over the world under the umbrella of research in "Human Biology" and gave rise to one of the standard texts for research into the human biological sciences. The original "*IBP Handbook*",[10] revised and renamed "*Practical Human Biology*" in its second edition,[11] forms the source for many scientists who wish to use standard techniques to measure growth. Its value is in its acceptance, by many, as the source, not only for techniques of anthropometric measurement but also for many other techniques that are applied in research in human biology such as dermatoglyphics, physiological measures, salt and water balance, thermal comfort, nutritional status, etc. The development of digital technology has brought with it advantages in anthropometric instrumentation which will make the practice of reading instruments, calling out numbers, and recording these numbers by hand virtually obsolete in the future. However, the measurement of human growth is still characterized by an observer using non-digital instruments to measure children although software developments have allowed data recording, editing and analysis to become an automated process and put sophisticated analytical procedures at the fingertips of most research workers.

A final note in this context must concern the problems inherent in measuring growth. The fact that accurate instrumentation has overcome many of the errors inherent in anthropometry does not mean that the greatest source of error is not still the measurer her/himself. The qualities outlined over 70 years ago by the anthropologist Aleš Hrdlička,[12] are still relevant today: good eyesight for distance and color, freedom from halitosis and other unpleasant odors, sympathy, perseverance, orderliness, thorough honesty and carefulness. The anthropometrist should be "careful of the sensibilities of his subjects; careful in technique, careful in reading the scale of his subject, careful in recording and

capable of concentration on his work".[12] To Hrdlička's essential qualities must be added basic qualifications in the sciences of anatomy, physiology and physics. Also, because of the extremely numerical nature of anthropometry, the anthropometrist must be numerate and have studied some basic statistical methods. So, accurate measurement is not just about the instrument, it is also about the person using the instrument.

While the methods described in this chapter are those of classical anthropometry using hand-held instruments with linear scales, digital anthropometry using electronic instrumentation is evolving rapidly. In particular there is rapid development of relatively low-cost three-dimensional optical imaging technology within nutritional and body composition research.[13]

The context of measurement; screening, surveillance and monitoring

Our knowledge of the process of human growth and development is directly dependent on the methods employed to measure that process and the scientific and/or clinical context within which those methods are employed. The context will usually be one of three types: screening, surveillance, or monitoring.

Screening is concerned with the identification of a particular subset of the population with certain prescribed characteristics. Usually they will be outside (above or below) a certain cut-off point for height, weight, or a combination of the two such as weight-for-height or body mass index (BMI). Such cut-off points are replete within the literature pertaining to growth. Stunting, for example, is defined as a height-for-age Z-score of less than −2.[14] Overweight, using the UK reference charts,[15] is defined as a BMI-for-age greater than the 91st centile and obesity by a BMI-for-age greater than the 98th centile. These values correspond to BMI's of 25 and 30 at 18 years of age but to lesser values at younger ages. In the USA a "danger of overweight" is defined by a BMI greater than the 85th centile and "obesity" by a BMI greater than the 95th centile of CDC 2002 charts.[16] To identify children outside all of these cut-offs it is necessary to measure the dimension of interest with known accuracy and reliability. Without such knowledge the possibility of falsely classifying a child as normal when they are not (false negative), or unwell when they are not (false positive), is unknown. Screening is a cross-sectional, once-off activity and usually involves large samples of children. Once identification is complete it will lead on to further assessment or intervention. In this context of large sample sizes and the need for high levels of measurement efficiency, growth status may be characterized by only a few dimensions such as height and weight. Instrumentation tends to be basic and portable and assessment is undertaken by more than one observer with each one working independently.

Surveillance is concerned with assessing the process of growth on more than one occasion on a sample of children and may well follow a screening exercise. For instance, the

screening process may have identified a sub-sample of stunted children below −2 Z-scores for height-for-age. It is decided that such children are to partake in a nutritional supplementation program and that they will be re-assessed at some future date to see if their height-for-age Z-scores have improved. This situation is now termed surveillance and may involve re-assessment over several months and/or years. Clearly this context requires rather more attention to detail than the first. The samples tend to be smaller, the need for a more comprehensive description of growth requires more dimensions to be assessed, and the number of observers will be fewer with perhaps greater expertise. In addition, and because assessment on two or more occasions is required, accuracy and reliability of measurement will become more of an issue.

It may be that this process of surveillance leads to the identification of a child with an unusual pattern of growth and the decision is made to regularly reassess the child in a clinical situation with access to treatment regimes if a treatable disorder is diagnosed. This final context is termed *monitoring* and involves the long-term high-frequency assessment of a single child or small sample of children. This context requires a specialist setting with dedicated space, high quality instrumentation, and a broad range of dimensions to properly assess all aspects of the pattern of growth.

Screening provides only cross-sectional data but in the latter two scenarios the outcome includes both cross-sectional and longitudinal components. Knowledge is gained both of the current size of the child and of the growth rate i.e. the change of size over time or "growth velocity". The usefulness of the velocity data will be dependent on the period of time between assessments; too short and the outcome is marred by measurement error, diurnal variation, and short-term fluctuations characteristic of saltatory growth,[17] too long and any meaningful shorter-term fluctuations will not be noticed.

VIMAR: validity, instrumentation, minimum unit of measurement, accuracy, reliability

VIMAR is a pneumonic that succinctly describes the most important elements to be considered when designing an anthropometric scenario.

Validity relates to the appropriateness of the dimension to be assessed. For instance, the relationship between height and arm span is well recognized and has led to the development of regression equations to predict height from arm span[18]. However, if the dimension of interest is height, and height can be measured accurately and reliably, then its estimation or prediction from other dimensions introduces an unnecessary source of error. In all cases the dimension of interest ought to be measured and not predicted from another dimension as this is a more valid description of the dimension.

Instrumentation prompts the observer to consider whether the instrument of choice is best able to measure the dimension of interest. For instance, an infant length measuring board is designed to measure the supine length of infants and produces more accurate and reliable data than using a tape measure.

Minimum unit of measurement relates to the smallest unit of measurement on the chosen instrument. For instance, stadiometers, used to measure height, usually have their smallest unit as millimetres, although some will have a minimum unit of centimetres. Clearly the minimum unit of measurement has important implications for both the accuracy and reliability of measurement. An important consideration in choosing the instrumentation is whether the minimum unit of the instrument is appropriate for the dimension to be measured and the reliability with which it can be measured. If the research question relies on knowing height to the nearest centimetre then instrumentation with a minimum unit of 1.0 cm will suffice.

Accuracy is defined by the Oxford English Dictionary as being "… in exact conformity with truth." Within an anthropometric context we do not know what "truth" is. For example, when we measure a child's height, we only have the estimation of that height, we do not know what the actual, true height is. We can improve the accuracy and decrease error by ensuring that we use a valid, specifically designed instrument, with appropriate precision and by using a properly trained observer.

Reliability (also known as precision) is the extent to which an observer or instrument consistently and accurately measures a particular dimension. Reliability involves three sources of error: the observer, the instrument, and the subject. Also, reliability involves two characteristics: consistency and accuracy. Reliability can be assessed in a test-retest experimental design by calculating both the Standard Error of Measurement (Smeas) (or Technical Error of Measurement (TEM)) and the Standard Deviation of Differences (S_d).[1,5,19]

Frequency of measurement

Within the measurement of human growth it is important to know ones accuracy and reliability both for the absolute (cross-sectional) determination of a child's size and for the determination of growth (rate of change with time). The measurement of growth and determination of growth velocity over two time points are affected by two sources of error, one for each measurement. The interval between measurement occasions will be determined, to some extent by the reliability of the observer. If, for instance, the observer has a reliability, or Standard Deviation of Differences (S_d), (or Technical error of Measurement (TEM)) of 0.3 cm and the child is growing at a rate of 4 cm year^{-1} then

growth will not be certain to have occurred (with 95% confidence) until the difference in heights between two measurement occasions is greater than 1.96×0.3 cm, or 0.59 cm i.e. greater than the 95% confidence limits. It will take this child 54 days to grow 0.6 cm thus measurements taken on a monthly or even two-monthly basis will be subject to observer error. The minimal time between measurement occasions for this child should be at least three months to avoid observer error and the maximum frequency of measurement is four times per year.

Measurements

This chapter will provide descriptions of how to measure the common dimensions that describe human growth. Lengthy discussions of instrumentation and variation in measuring techniques may be found in Cameron[1–5] and Lohman, Roche and Martorell.[19] The organization of this chapter is such that a measurement technique is described with the instrumentation recommended for the most accurate and reliable results. The measurements chosen for description are those that are recommended either as baseline measurements (e.g. height, weight, skinfolds) or as examples of measurement techniques that may be applied to other similar dimensions. Thus, where appropriate, such as for skinfolds and girths or circumferences, a generic technique is described that can be applied to any assessment site as well as specific techniques for the recommended sites. For example, a generic technique for the assessment of subcutaneous fat is described and specific techniques for the triceps, biceps, subscapular and suprailiac sites. These four sites are the most commonly measured, but you may wish to increase the number of sites because you are undertaking a more extensive investigation of fat patterning or have a particular interest in fat distribution. In that case the generic technique can be applied to any skinfold site as long as the site is accurately identified. The following measurements will be described followed by the recommended instruments to obtain accurate values: Linear dimensions: stature, sitting height, bi-acromial diameter, bi-iliac diameter; Circumferences/girths: head, arm, waist and hip; Skinfolds: triceps, biceps, subscapular and suprailiac; Weight. Finally, a glossary of anatomical surface landmarks is provided.

The accuracy with which these measurements may be obtained can be maintained at a high level by following a few simple rules of procedure:

1. Ensure that the subject is in the minimum of clothing or at least in clothing that in no way interferes with the identification of surface landmarks.
2. Familiarize the subject with the instrumentation, which may appear frightening to the very young subject, and ensure that he/she is relaxed and happy. If necessary, involve the parents to help in this procedure by conversing with the child.
3. Organize the laboratory so that the minimum of movement is necessary and so that the ambient temperature is comfortable and the room well lit.

4. When possible use another person to act as a recorder who will complete a measurement form. Place the recorder in such a position that he or she can clearly hear the measurements and is seated comfortably at a desk with enough room to hold recording forms, charts, and so on.
5. Measure the left-hand side of the body unless the research project protocol dictates that the right-hand side should be used or unless comparative projects have used the right-hand side.
6. Mark the surface landmarks with a water-soluble felt-tip pen prior to starting measurements.
7. Apply the instruments gently but firmly. The subject will tend to pull away from the tentative approach but will respond well to a confident approach.
8. Call out the results in whole numbers—for example, a height of 112.1 cm should be called out as "one, one, two, one" not as "one hundred and twelve point one" nor as "eleven, twenty-one". Inclusion of the decimal point may lead to recording errors and combinations of numbers may sound similar, for example, "eleven" may sound like "seven".
9. Establish the reliability of measurement (accuracy and repeatability) prior to the study using subjects with similar characteristics (age, sex, etc.) to the participants in the study proper.
10. During the study create a quality control procedure by repeating measurements on randomly selected subjects. At the end of each session these can be compared to the *a priori* reliability figures obtained in the pilot study.
11. When measurements are repeated e.g. skinfolds, the recorder should check that the repeat value is within the known reliability of the observer. If it is not, a third measurement is indicated. For a final value average the two that fall within the limits.
12. Do not try to measure too many subjects in any one session. Fatigue will detract from reliable measurement for which concentration is vital.

Stature (harpenden stadiometer, martin or GPS anthropometer, wall mounted or rigid stadiometer)

The subject presents for the measurement of stature dressed in the minimum of clothing, preferably just underclothes, but if social custom or environmental conditions do not permit this then at the very least without shoes and socks. The wearing of socks will not, of course, greatly affect height, but socks may conceal a slight raising of the heels that the observer from his/her upright position may not notice.

The subject is instructed to stand upright against the stadiometer such that his/her heels, buttocks and scapulae are in contact with the backboard, and the heels are together (Fig. 11.1). If the subject suffers from "knock-knees" then the heels are slightly spread so

Fig. 11.1
The measurement of stature.

that the knees touch, but do not overlap. As positioning is of the greatest importance the observer should always check that the subject is in the correct position by starting with the feet and checking each point of contact with the backboard as he/she moves up the body. Having got to the shoulders he/she then checks that they are relaxed, by running his/her hands over them and feeling the relaxed trapezius muscle. The observer then checks that the arms are relaxed and hanging loosely at the sides. The head should be positioned in the "Frankfurt Plane" (the lower orbits of the eyes and the external auditory meatii are in a horizontal line), and the headboard of the instrument is then moved down to make contact with the vertex (highest point in the midline) of the skull. With the subject in the correct position he/she is instructed: "Take a deep breath and stand tall." This is done to straighten out any kyphosis or lordosis and produce the greatest unaided height. It is at this point that the observer applies pressure to the mastoid processes – not to physically raise the head but to hold it in the position that the subject has lifted it to by breathing deeply. The subject is then instructed to "Relax" or to "Let the air out" and "Drop the shoulders". The shoulders are naturally raised when the subject takes a deep breath and thus tension is increased in the spinal muscles and prevents total elongation of the spine. Relaxing or breathing out releases this tension and commonly produces an increase of about 0.5 cm in absolute height. The effect of this pressure or traction technique is to counteract the effect of diurnal variation that works to reduce stature during the normal course of a day. Stature

is read to the last completed unit whether from a counter or graduated scale. Height is not rounded up to the nearest unit as this will produce statistical bias and almost certainly invalidate estimates of height velocity.

Sitting-height (sitting-height table or martin or GPS anthropometer)

Accurate measurement of sitting-height requires impeccable positioning from the subject and, therefore, great attention to detail from the observer. Whether on a specially constructed sitting-height table, or a suitable flat surface, the subject is positioned so that the head is in the Frankfurt Plane, the shoulders relaxed, the back straight, the upper surface of the thighs horizontal and the feet supported so that a right angle is formed with the thighs and the tendons of the biceps femoris, at the back of the knee, are just clear of the table. The arms are loose at the sides and the hands rest in the subject's lap (Fig. 11.2).

Each part of this position may be checked, as for stature, by starting at the feet and moving up to the head. It is essential to have the knees raised away from the table but only to the point where a right angle is formed with the thighs. Too acute an angle tends to cause the subject to roll backwards, and too obtuse an angle or the thighs touching the table tends to roll the subject forwards. Both situations reduce sitting-height, and prevent

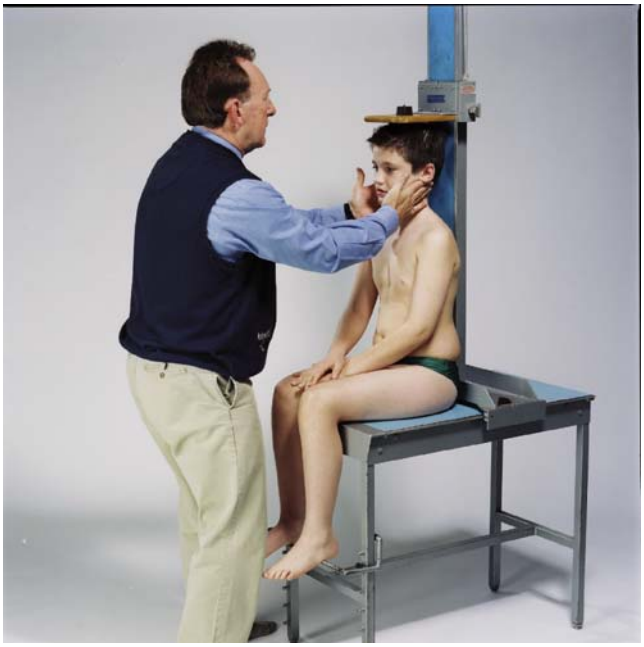

Fig. 11.2
The measurement of sitting-height.

the subject from maintaining a straight back. If the subject's hands are not resting in his/her lap or along his/her thighs then he may use them to push himself from the surface of the table and falsely increase sitting-height. Similarly, contraction of the thighs or buttocks will raise the subject away from the table. The straightness of the back is the most difficult part to accomplish but may be achieved by giving the subject clear instructions to, for instance, "Sit up straight" or "Sit tall" and at the same time running the fingers up the spine from the sacrum to the thoracic vertebrae causing the subject to involuntarily move away from the observer's hand and thus straighten any slouching or rounding of the spine common to most subjects when asked to sit. Having lowered the headboard the subject is instructed to "Take a deep breath and relax." Pressure is applied to the mastoids to prevent the head from falling on relaxation and the measurement read to the last completed unit.

Bi-acromial diameter (harpenden, martin, or GPS anthropometer)

Bi-acromial diameter is the distance between the tips of the acromial processes. It is measured from the rear of the subject with the anthropometer. The position of the lateral tips of the acromials is slightly different in each subject and it is therefore necessary for the observer to carefully palpate their exact position in each subject before applying the instrument. This is most easily done with the subject standing with his back to the observer such that the observer can run his hands over the shoulders of the subject. This tactile awareness of the position of the acromials is an important part of the measurement procedure because it allows the observer to be confident of the measurement points when he applies the instrument. Having felt the position of the acromia and that the subject's shoulders are relaxed, the observer applies the anthropometer blades to the lateral tips of the processes (Fig. 11.3).

The anthropometer is held so that the blades rest medially to the index fingers and over the angle formed by the thumb and index finger. The index fingers rest on top of the blades, to counteract the weight of the bar and counter mechanism, and the middle fingers of each hand are free to palpate the measurement points immediately prior to measurement. In this position the observer can quite easily move the blades of the anthropometer so long as it is of the counter type. Other anthropometers have too great a frictional force opposing such easy movement and must be held by the main bar so that the blades are remotely applied to the marked acromial processes. The blades must be pressed firmly against these protuberances so that the layer of tissues which covers them is minimized. To ensure that the correct measurement is being made it is a simple matter to roll the blades up and over the acromia and then outwards and downwards so that the observer feels the blades drop over the ends of the acromia.

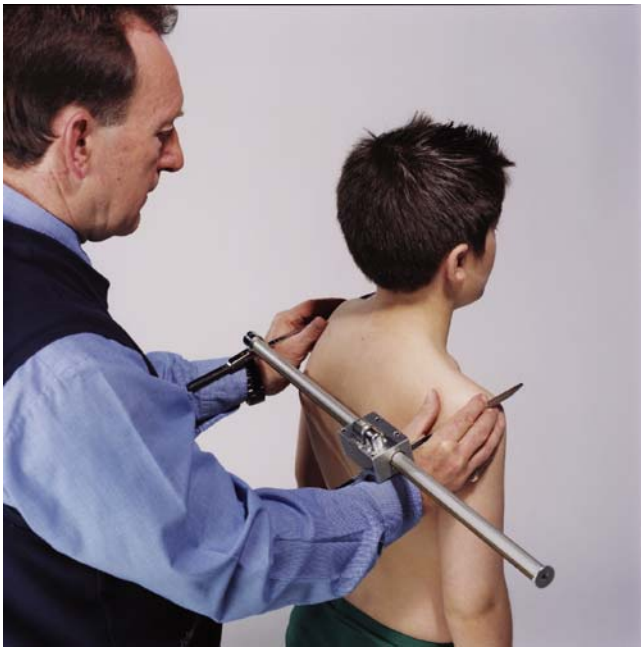

Fig. 11.3
The measurement of biacromial diameter.

Bi-iliac diameter (harpenden, martin, or GPS anthropometer)

The subject stands with his/her back to the observer, feet together and hands away from his/her sides to ensure a clear view of the iliac crests. For measurements depending on the identification of any bony landmark (e.g. bi-acromial diameter) it is a good procedure for the observer to feel the position and shape of the landmark prior to measurement. Thus in this case the iliac crests should be palpated prior to applying the instrument, especially when the subject has considerable fat deposits in that region. The anthropometer is held so that the blades rest medially to the index fingers and over the angle formed by the thumb and index finger. The index fingers rest on top of the blades, to counteract the weight of the bar and counter mechanism, and the middle fingers of each hand are free to palpate the measurement points immediately prior to measurement. In this position the observer can quite easily move the blades of the anthropometer so long as it is of the counter type. Other anthropometers have too great a frictional force opposing such movement and must be held by the main bar so that the blades are remotely applied to the most lateral points of the iliac crests. This will be more easily accomplished if the anthropometer is slightly angled downwards and the blades applied to the crests at a point about 2–3 cm from the tips (Fig. 11.4).

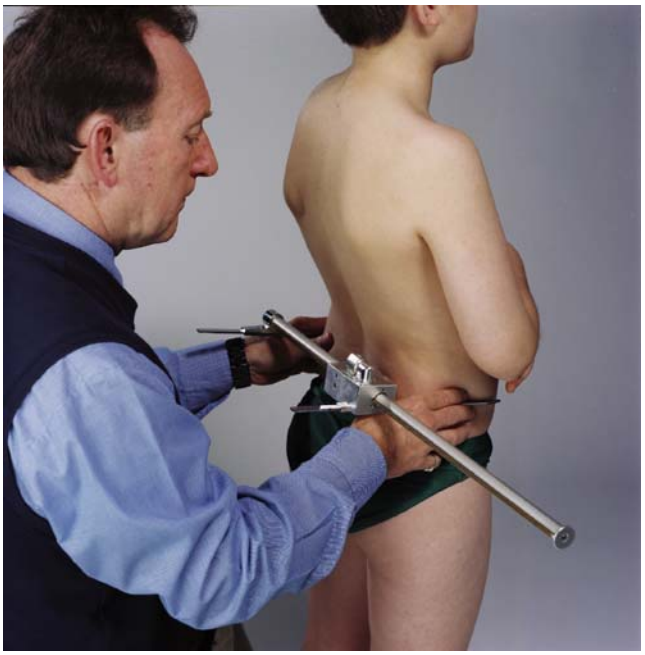

Fig. 11.4
The measurement of bi-iliac diameter.

To ensure that the most lateral points have been obtained it is a useful point of technique to 'roll' the blades over the crests. It will be seen on the counter of the instrument that at a particular point the distance between the crests is greatest; this is the point of measurement.

Circumferences/girths

Head circumference (tape measure)

Head circumference used to be described as a "fronto-occipital" circumference or a "Frankfurt Plane" circumference, but both techniques have largely been replaced by simply measuring the maximum head circumference (Fig. 11.5).

The subject stands sideways to the observer such that the left hand side is closer. The head is held straight or in the Frankfurt Plane but the plane is of little consequence as long as the head is straight and the eyes looking forward. The subject's arms are relaxed. It is easier for the observer if he/she is positioned so that his/her eyes are level with the subject's. The tape is opened and passed around the head from left to right. The free and fixed ends are then transferred to the opposite hands so that the tape now passes completely around the head and crosses in front of the-observer. Using the middle finger of the left hand the observer presses the loose tape to the forehead of the child and moving

Fig. 11.5
The measurement of head circumference.

the finger up and down determines the most anterior part of the head. Having done this he pulls the tape tighter and repeats this procedure with the middle finger of the right hand to determine the most posterior part of the occiput. Once determined, the tape is pulled tight to compress the hair and the measurement read to the last completed unit. Head circumference is the only circumference in which the tape is pulled tight and even then should cause the child no undue discomfort. It is essential to remove any headgear or ornamentation that will get in the way of the tape measure.

Arm circumference or mid-upper arm circumference (tape measure)

The subject stands in the same position as for head circumference measurement; sideways with the left arm hanging loose at his side. The mid-arm level is determined as the mid-point between the acromion and olecranon with the arm flexed at a right angle (see page XX). The tape is passed around the arm from left to right and the free and fixed ends transferred from one hand to the other. Ensuring that the tape is at the same level as the mid upper-arm mark, it is tightened so that it touches the skin all round the circumference but does not compress the tissue to alter the contour of the arm. The circumference is then read to the last completed unit (Fig. 11.6).

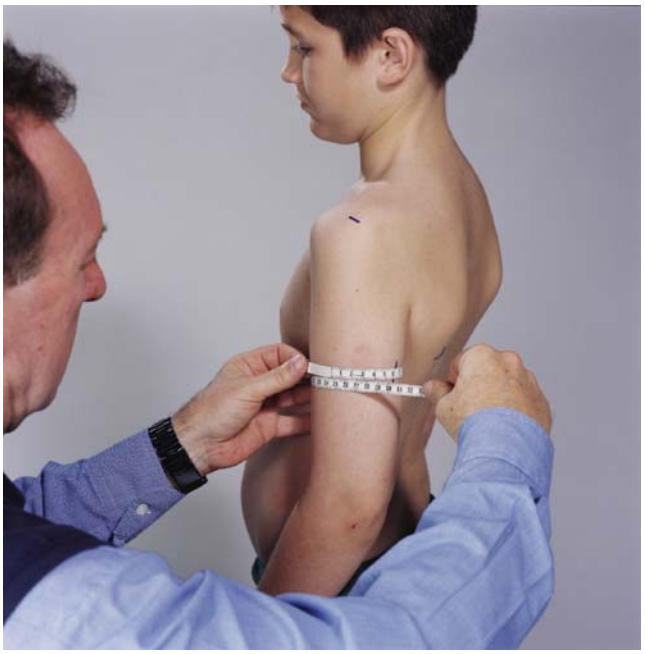

Fig. 11.6
The measurement of arm circumference.

Because the arm in cross-section is not an exact circle but rather oval, some difficulty is usually met in ensuring that the tape actually touches the skin on the medial side of the arm. To ensure that this is so the middle finger of the left hand can be used to gently press the tape to the skin.

Waist circumference or abdominal circumference (tape measure)

The measurement is taken at the minimum circumference between the iliac crests and lower ribs. The general technique is for the subject to stand erect facing the observer with the arms away from the body. The tape is passed around the body and tightened at the required level ensuring that it is horizontal and not compressing the soft tissue.

Hip circumference (tape measure)

Hip circumference should be measured at the level of the greatest protrusion of the buttocks when the subject is standing erect with the feet together. The subject stands sideways to the observer with the feet together and arms folded. The observer passes the tape around the body at the level of the most prominent protrusion of the buttocks so that it lightly touches but does not compress the skin.

Skinfolds (harpenden, holtain, or lange calipers)

The technique of picking up the fold of subcutaneous tissue measured by the skinfold caliper is often referred to as a "pinch" but the action to obtain the fold is to sweep the index or middle finger and thumb together over the surface of the skin from about 6 to 8 cm apart. This action may be simulated by taking a piece of paper and drawing a, say, 10 cm line on its surface. If the middle finger and thumb are placed at either end of this line and moved together such that they do not slide over the surface of the paper but form a fold of paper between them then that is the action required to pick up a skinfold. To 'pinch' suggests a small and painful pincer movement of the fingers and this is not the movement made. The measurement of skinfolds should not cause undue pain to the subject, who may be apprehensive from the appearance of the calipers and will tend to pull away from the observer, and, in addition, a pinching action will not collect the quantity of subcutaneous tissue required for the measurement.

Triceps skinfold

The level for the triceps skinfold is the same as that for the arm circumference - mid-way between the acromion and the olecranon when the arm is flexed at a right angle. It is important that the skinfold is picked up both at a midpoint on the vertical axis of the upper-arm and a midpoint between the lateral and medial surfaces of the arm. If the subject stands with his back to the observer and bends the left arm the observer can palpate the medial and lateral epicondyles of the humerus. This is most easily done with the middle finger and thumb of the left hand, which will eventually grip the skinfold. The thumb and middle finger are then moved upwards, in contact with the skin, along the vertical axis of the upper-arm until they are at a level about 1.0 cm above the marked midpoint. The skinfold is then lifted away from the underlying muscle fascia with a sweeping motion of the fingers to the point at which the observer is gripping the "neck" of the fold between middle finger and thumb (Fig. 11.7).

The skinfold caliper, which is held in the right hand with the dial upwards, is then applied to the neck of the skinfold just below the middle finger and thumb at the same level as the marked midpoint of the upper arm. The observer maintains his/her grip with the left hand and releases the trigger of the skinfold caliper with his right to allow the caliper to exert its full pressure on the skinfold. In almost every case the dial of the caliper will continue to move but should come to a halt within a few seconds at which time the reading is taken to the last completed 0.1 mm. In larger skinfolds the caliper may take longer to reach a steady state but it is unusual for this to be longer than 7 s. Indeed, if the caliper is still moving rapidly it is doubtful that a true skinfold has been obtained and the observer must either try again or admit defeat. This situation is only likely to occur in the more obese

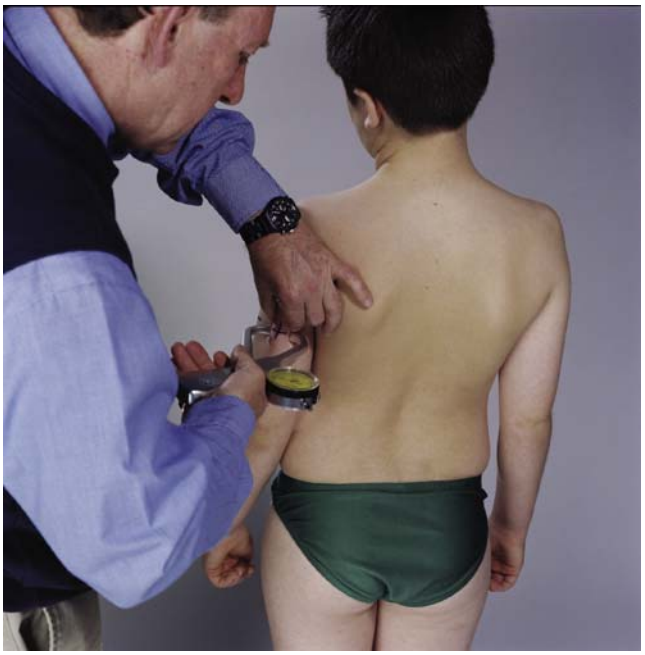

Fig. 11.7
The measurement of triceps skinfold.

subject with skinfolds greater than 20−25 mm - that is, above the 97th centile of British charts. Within the 97th and third centiles skinfolds are relatively easy to obtain but they do require a great deal of practice.

Biceps skinfold

The biceps skinfold is the exact opposite of the triceps skinfold, being on the anterior aspect of the arm and at the same midpoint level as previously described for triceps skinfold. It is picked up with the subject facing the observer and his/her left arm hanging relaxed but with the palm facing forwards (Fig. 11.8).

The middle finger and thumb sweep together at a point 1 cm above the marked midpoint level coming together at the vertical axis joining the center of the anticubital fossa and the head of the humerus. It is unusual for the movement of the dial to present any problem with this skinfold measurement, as it is not a site for major fat deposits.

Subscapular skinfold

The point of measurement is located immediately below the inferior angle of the scapula. The subject stands with his/her back to the observer and his/her shoulders relaxed and

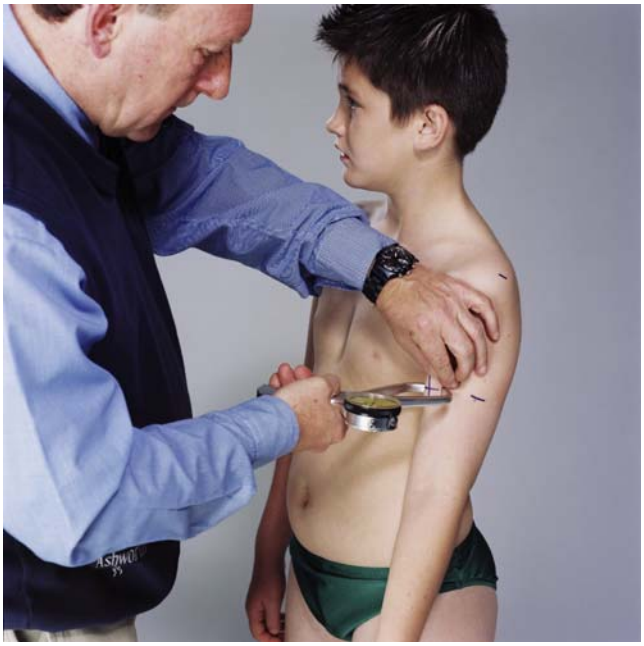

Fig. 11.8
The measurement of biceps skinfold.

arms hanging loosely at the sides of the body. This posture is most important to prevent movement of the scapulae; if the subject folded his/her arms, for instance, the inferior angle of the scapula would move laterally and upwards and therefore no longer be in the same position relative to the layer of fat. The skinfold is picked up, as for triceps skinfold, by a sweeping motion of the middle finger and thumb, and the caliper applied to the neck of the fold immediately below the fingers (Fig. 11.9).

The fold will naturally be at an angle laterally and downwards and will not be vertical. Once again, the dial of the caliper will show some movement that should soon cease.

Supra-iliac skinfold

The point of measurement for the supra-iliac skinfold is 1 cm superior and 2 cm medial to the anterior superior iliac spine. This is best palpated with the subject standing facing the observer. The skinfold is picked up with a sweep of the middle finger and thumb and is a vertical skinfold (Fig. 11.10).

Once again the caliper is applied below the fingers and, after the dial has stopped moving, the measurement is read to the last completed 0.1 mm. It should be noted that Durnin and Rahaman[20] and Durnin and Womersley,[21] who developed linear regression equations that

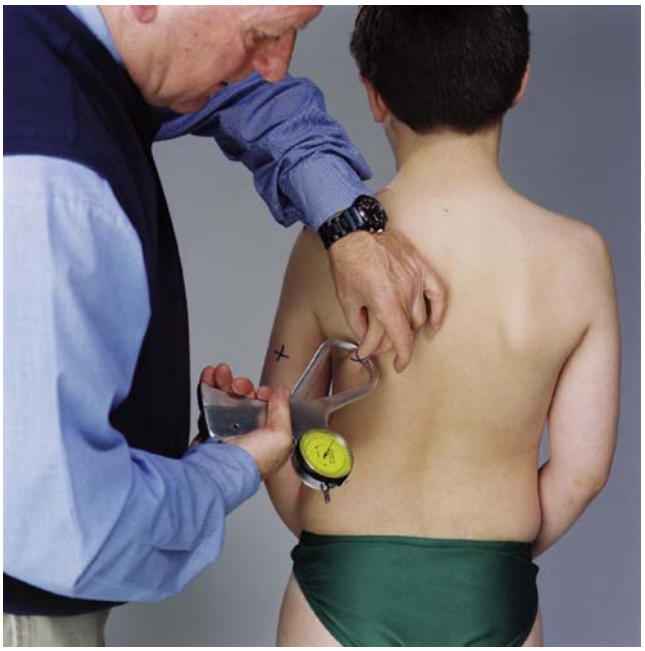

Fig. 11.9
The measurement of subscapular skinfold.

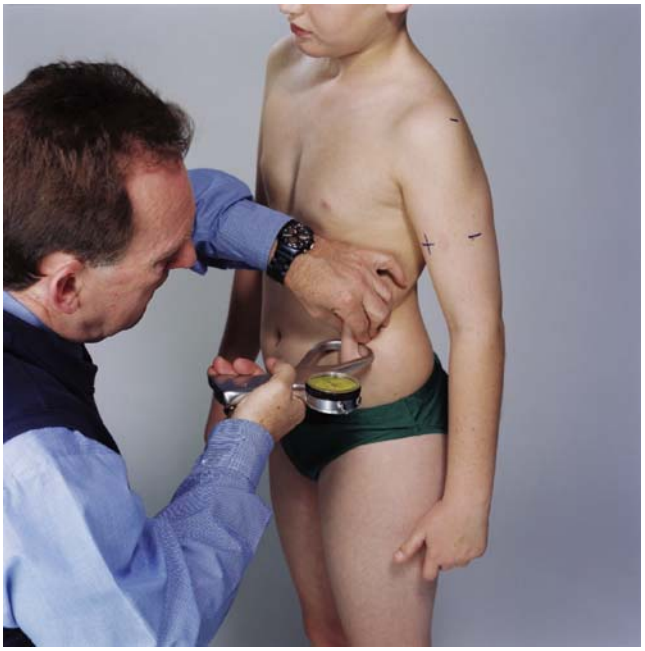

Fig. 11.10
The measurement of supra-iliac skinfold.

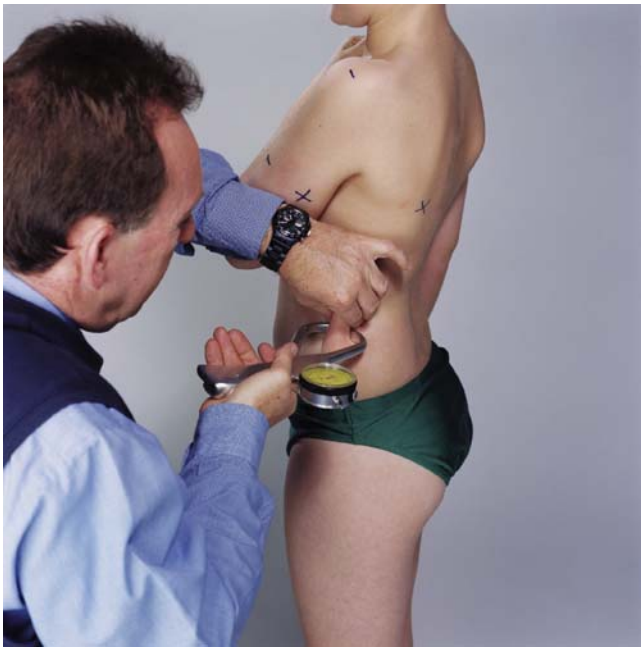

Fig. 11.11
The measurement of mid-axillary supra-iliac skinfold.

are frequently used to predict total body fat from skinfolds, do not use this conventional supra-iliac site for their measurement to derive total body fat. Instead they use a *mid-axillary* supra-iliac skinfold just above the iliac crest but still vertical (Fig. 11.11).

Weight (digital weighing scales or beam balance)

The measurement of weight should be the simplest and most accurate of the anthropometric measurements. Assuming that the scales are regularly calibrated, the observer ensures that the subject is either dressed in the minimum of clothing or a garment of known weight that is supplied by the observer. The subject stands straight, but not rigid or in a "military position", and is instructed to "stand still". If the instrument is a beam balance then the observer moves the greater of the two counter-weights until the nearest 10 kg point below the child's weight is determined. The smaller counter-weight is then moved down the scale until the nearest 100 g mark below the point of over balance is reached and this is recorded as the true weight. This procedure is necessary to determine weight to the *last completed unit*. If the weight is taken as the nearest 100 g above true weight then that 100 g is greater than actual weight and the last unit has not been completed.

While baby scales are available inmost contexts, the determination of the weight of neonates can be a noisy and tearful procedure but need not be if the help of the mother is solicited. The observer simply weighs mother and child together and then transfers the baby to his/her assistant's arms and weighs the mother by herself. The baby's weight can thus be determined by difference − (weight of mother + baby) − (weight of mother) − and the child is left relatively undisturbed.

Surface landmarks

Acromion process (lateral border of the acromion) (Fig. 11.12)

The acromion projects forwards from the lateral end of the spine of the scapula with which it is continuous. The lower border of the crest of the spine and the lateral border of the acromion meet at the acromial angle, which may be the most lateral point of the acromion. Great diversity in the shape of the acromion between individuals means that sometimes the acromial angle is not the most lateral point. Palpation of the most lateral

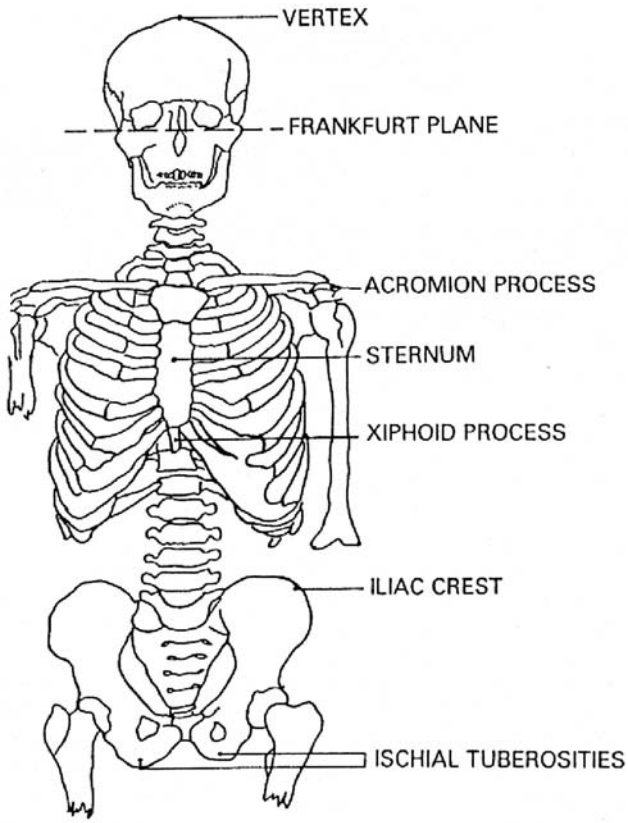

Fig. 11.12
Skeletal landmarks of the skull, thorax, pectoral and pelvic girdles.

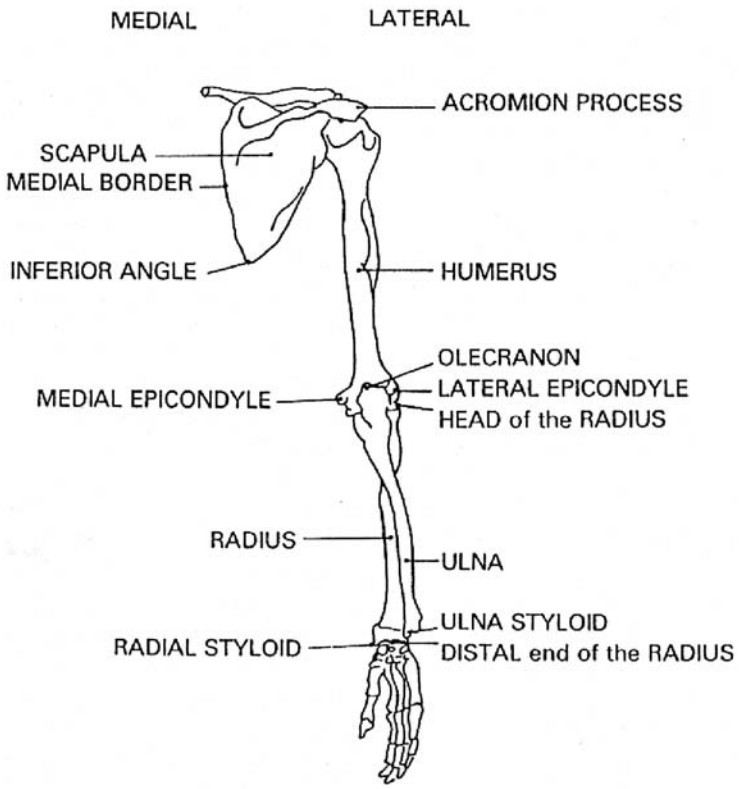

Fig. 11.13
Skeletal landmarks of the scapular and upper limb (posterior view).

part may best be performed by running the anthropometer blades laterally along the shoulders until they drop below the acromia. If the blades are then pushed medially the most lateral part of the acromia must be closest to the blades and may be felt below the surface marks left by the blades. There is the possibility of the inexperienced anthropometrists confusing the acromio-clavicular joint with the lateral end of the acromion. Great care must be taken to distinguish between these two landmarks prior to measurement.

Anterior superior iliac spine (Fig. 11.15)

This is the anterior extremity of the ilium which projects beyond the main portion of the bone and may be palpated at the lateral end of the fold of the groin. It is important to distinguish the iliac crest from the anterior spine when measuring bi-iliac diameter (see Bi-iliac Diameter, page XX).

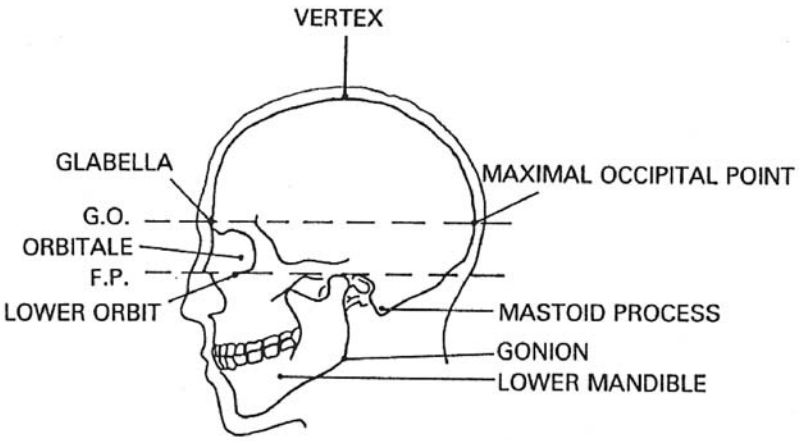

Fig. 11.14
Skeletal landmarks of the skull.

Biceps brachii

The biceps brachii is the muscle of the anterior aspect of the upper arm. Its two heads, the short and the long, arise from the coracoid process and the supraglenoid tubercle of the scapula respectively and are succeeded by the muscle bellies before they end in a flattened tendon that is attached to the posterior part of the radial tuberosity. When relaxed the muscle belly has its greatest bulge toward the radius but when contracted with the arm flexed the belly rises to a point nearer the shoulder. Thus relaxed and contracted arm circumferences, taken at the maximum bulge of the muscle, are not at exactly the same level.

Distal end of the radius (Fig. 11.13)

This is the border of the radius proximal to the distal-superior borders of the lunate and scaphoid and medial to the radial styloid. It may be palpated by moving the fingers medially and proximally from the radial styloid (see 'Radial Styloid', below).

External auditory meatus

This landmark, used to obtain the Frankfurt Plane, is also called the external acoustic meatus and leads to the middle ear from the external auricle. In terms of a surface

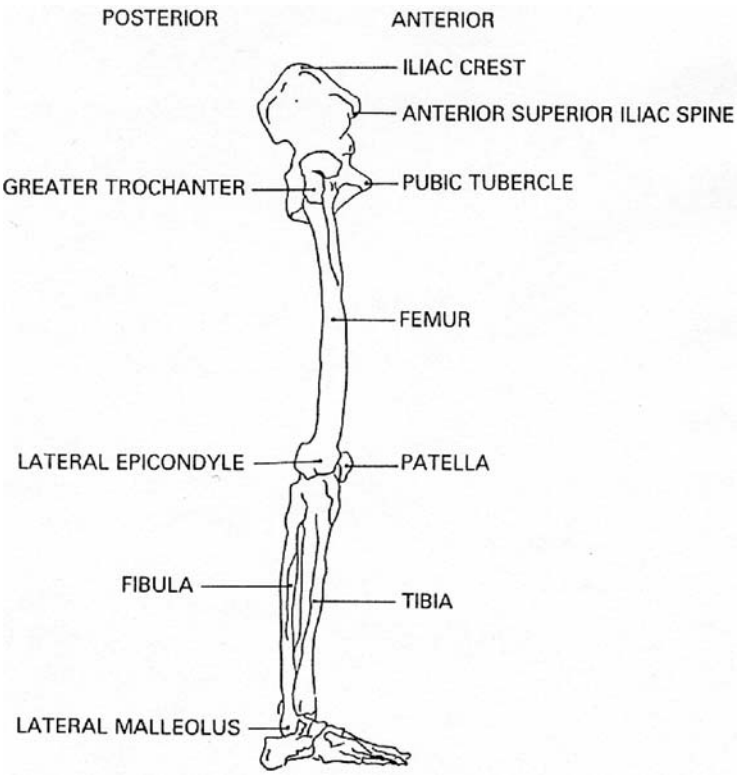

Fig. 11.15
Skeletal landmarks of the pelvis and lower limb (lateral view).

landmark it is therefore simply present as a hole in the external ear and may therefore be easily seen. The tragus, the small curved flap that extends posteriorly from the front of the external ear, overlaps the orifice of the meatus and may be used to gauge the level of the orifice.

Femur epicondyles (Fig. 11.15)

The lower end of the femur consists of two prominent masses of bone called the condyles, which are covered by large articular surfaces for articulation with the tibia. The most prominent lateral and medial aspects of the condyles are the lateral and medial epicondyles. These may be easily felt through the overlying tissues when the knee is bent at a right angle, as in the sitting position. If the observer's fingers are then placed on the medial and lateral aspects of the joint the epicondyles are the bony protuberances immediately above the joint space.

Frankfurt Plane (Fig. 11.12)

This plane, used extensively in anthropometric measurement, is obtained when the lower margins of the orbital openings and the upper margins of the external acoustic (auditory) meatus lie in the same horizontal plane. The supinated Frankfurt Plane, used in the measurement of recumbent and crown-rump length, is vertical rather than horizontal.

Gastrocnemius

This is the most superficial of the group of muscles at the rear of the lower leg and forms the belly of the calf.

Glabella (Fig. 11.14)

This landmark is in the midline of the forehead between the brow ridges and may be used as the most anterior point of the head.

Gluteal fold

This fold or furrow is formed by the crossing of the gluteus maximus and the long head of the biceps femoris and semitendinosus. It may therefore be viewed from the lateral aspect or the posterior aspect as the crease beneath the buttock. In some subjects, perhaps because of a lack of gluteal development, a crease may not be present. In this case the level of the gluteal fold is judged from the lateral profile of the buttocks and posterior thigh.

Head of the radius (Fig. 11.13)

This may be palpated as the inverted, U-shaped bony protuberance immediately distal to the lateral epicondyle of the humerus when the arm is relaxed with the palm of the hand facing forwards.

Humeral epicondyles (Fig. 11.13)

These are the non-articular aspects of the condyles on the lower surface of the humerus. The medial epicondyle forms a conspicuous blunt projection on the medial aspect of the elbow when the arm is held at the side of the body with the palm facing forward. The lateral epicondyle may be palpated opposite and a little above the medial epicondyle.

Iliac crest (Fig. 11.15)

This may be palpated as the most superior edge of the ilium and may be easily felt through the overlying soft tissue. Greater difficulty will be experienced with the more obese subject but it is quite possible with the anthropometer blades to compress the tissue and feel the crest.

Malleoli (Fig. 11.15)

The medial malleolus is the bony protuberance on the medial side of the ankle. It is the inferior border of this malleolus that is palpated and used as a landmark for the measurement of tibial length.

Mastoid process (Fig. 11.14)

This is the conical projection below the mastoid portion of the temporal bone. It may be palpated immediately behind the lobule of the ear and is larger in the male than in the female.

Mid-axillary line

The axilla is the pyramidal region situated between the upper parts of the chest wall and the medial side of the upper arm. The mid-axillary line is normally taken as the line running vertically from the middle of this region to the iliac crest.

Mid-inguinal point (inguinal crease)

The inguinal ligament runs from the anterior superior iliac spine to the pubic tubercle at an angle of 35–40° and is easily observed in all individuals. The mid-point between the anterior spine and the pubic tubercle on the line of the inguinal ligament is taken as the mid-inguinal point.

Mid point of the arm

The mid point of the arm, used for arm circumference, is taken as the point on the lateral side of the arm midway between the lateral border of the acromion and the olecranon when the arm is flexed at 90°. This may be most easily determined by marking the lateral border of the acromion and applying a tape measure to this point.

If the tape is allowed to lie over the surface of the arm, the mid-point may easily be calculated and marked. Alternatively, tape measures do exist with a zero mid-point that are specifically designed to determine this landmark. It has been common to refer to this point, and the circumference or girth at this level, as the "mid upper-arm" landmark/ circumference.

Occiput (Fig. 11.14)

The occipital bone is situated at the back part and base of the cranium. The occiput is the most posterior part of this bone and may be clearly seen from the side view of the subject.

Olecranon (Fig. 11.13)

The olecranon is the most proximal process of the ulna and may be easily observed when the arm is bent as the point of the elbow.

Patella (Fig. 11.15)

The patella is the sesamoid bone in front of the knee joint embedded in the tendon of the quadriceps muscle. It is flat, triangular below and curved above. When the subject is standing erect its lower limit lies above the line of the knee joint and its upper border may be palpated at the distal end of the quadriceps muscle.

Pinna of the ear

The pinna of the ear is more correctly called the lobule and is the soft part of the auricle that forms the ear-lobe.

Radial styloid (Fig. 11.13)

The radial styloid is the distal projection of the lateral surface of the radius. It extends toward the first metacarpal and may be palpated as a bony projection on the lateral surface of the wrist when the hand is relaxed.

Scapula (Fig. 11.13)

The scapula is the large, triangular flattened bone on the posterolateral aspect of the chest, and is commonly known as the shoulder blade. Its medial border slopes downwards and laterally to the inferior angle that may be easily palpated, and lies over the seventh rib or seventh intercostal space when the arm is relaxed.

Sternum (Fig. 11.12)

The sternum or breastbone is the plate of bone inclined downwards and a little forwards at the front of the chest. It is composed of three parts; the manubrium at the top, the body or mesosternum at the center and the xiphoid process at the lower end. The mesosternum and xiphoid process are important landmarks in anthropometry. The mesosternum is marked by three transverse ridges or sternabrae and the junction between the third and fourth sternabrae form a landmark in chest measurement. The fourth sternabrae may not be easily palpated but the junction lies below the more easily palpated third sternabrae. The xiphoid process may be palpated by following the line of the sternum to its end. The sternum is considerably larger in males than in females.

Trapezius

The Trapezius is a flat, triangular muscle extending over the back of the neck and the upper thorax.

Triceps

The triceps muscle is the large muscle on the posterior side of the upper arm. When the arm is actively extended two of the three triceps heads may be seen as medial and lateral bulges.

Trochanters (Fig. 11.15)

The greater and lesser trochanters are projections at the proximal end of the femur. The lesser trochanter cannot be palpated on the living subject because it lies on the posterior surface of the femur and is covered by the large gluteal muscles. The greater trochanter, however, is palpable as the bony projection on the lateral surface of the upper thigh approximately a hand's breadth below the iliac crest.

Ulna styloid (Fig. 11.13)

The styloid process of the ulna is present as a short, rounded projection at the distal end of the bone. It may be easily palpated on the posterior-medial aspect of the wrist opposite and about 1 cm above the styloid process of the radius.

Umbilicus

The umbilicus, or naval, is clearly observable in the center of the abdomen. It is variable in position, lying lower in the young child due to lack of abdominal development.

Vertex of the skull (Fig. 11.14)

This is the top-most point of the skull and theoretically comes into contact with the stadiometer headboard when height is being properly measured. With the head in the Frankfurt Plane the vertex is slightly posterior to the vertical plane through the external auditory meatus and may be easily palpated.

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CHAPTER 12

Assessment of maturation

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Introduction

The process of maturation is continuous throughout life – it begins at conception and ends at death. This chapter will concentrate on the *assessment* of the process of maturation that is intimately linked to physical growth i.e. from birth to the end of adolescence. Because "growth" and "maturation" are usually spoken of synonymously it is important to differentiate between them. Bogin[1] defines growth as "a quantitative increase in size or mass" such as increases in height or weight. Development or maturation, on the other hand, is defined as "a progression of changes, either quantitative or qualitative, that lead from an undifferentiated or immature state to a highly organized, specialized, and mature state". The end-point of maturation, within the context of early life stages, is the attainment of adulthood, which I define as a "functionally mature individual". Functional maturation, in a biological context, implies the ability to successfully procreate and raise offspring who themselves will successfully procreate. We know that in addition to the obvious functional necessities of sperm and ova production, reproductive success within any mammalian society is also dependent on a variety of morphological characteristics such as size and shape. The too short or too tall, the too fat or too thin, are unlikely to achieve the same reproductive success as those within an "acceptable" range of height and weight values that are themselves dependent on the norms in a particular society. Thus in its broadest context, maturation *and* growth are intimately related and both must reach functional and structural endpoints that provide the opportunity for successful procreation.

Initial considerations

To understand how maturation can be assessed it is important to first appreciate that maturation is not linked to time in a chronological sense. In other words, one year of chronological time is not equivalent to one year of maturational "time". This is perhaps best illustrated in Fig. 12.1 in which three boys and three girls of precisely the same

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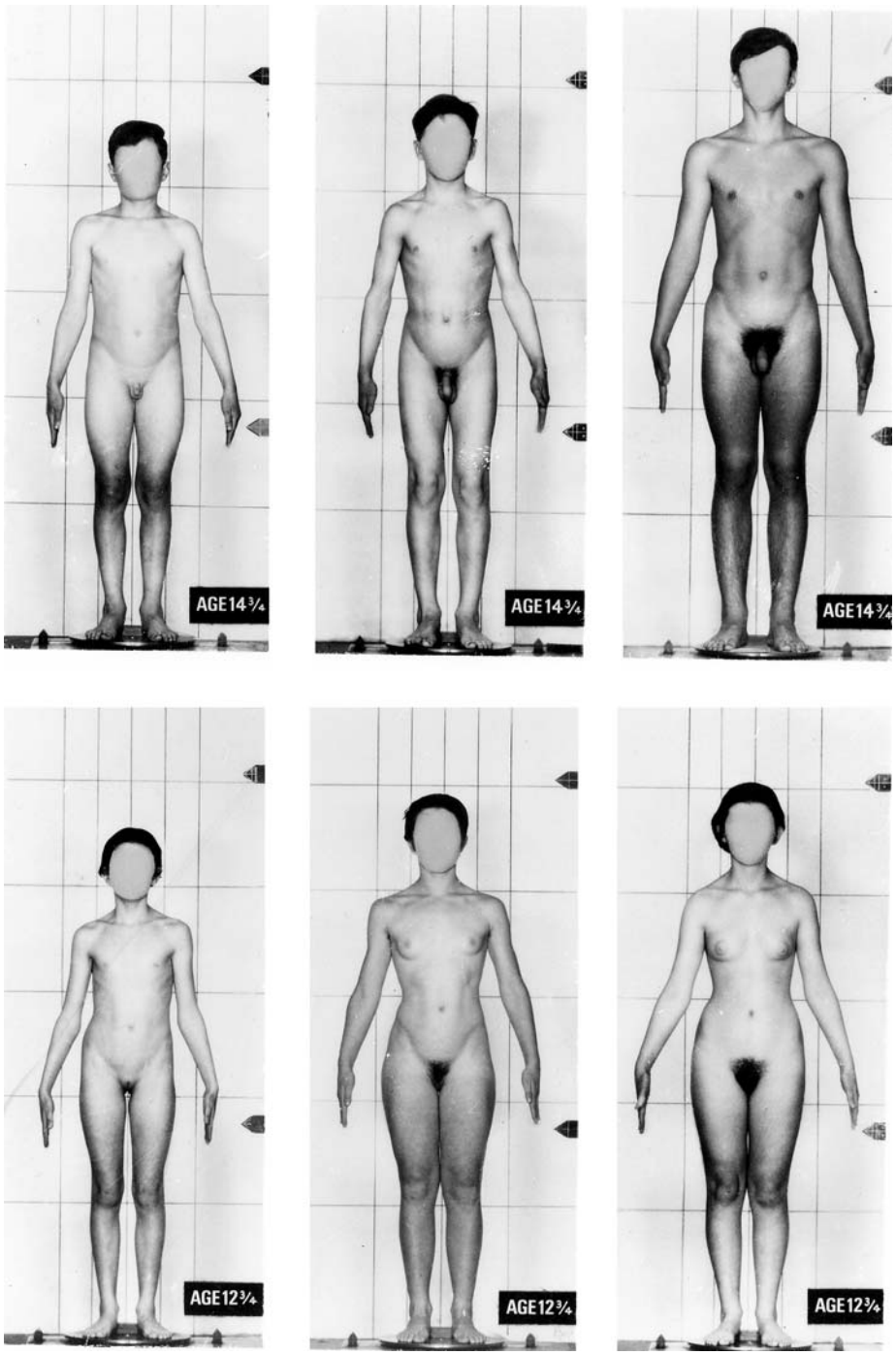

Fig. 12.1

Three boys and three girls photographed at the same chronological ages within sex; 12.75 years for girls and 14.75 years for boys. *From Tanner JM. Growth and endocrinology of the adolescent. In: Gardner L, eds.* Endocrine and Genetic Diseases of Childhood. *2nd ed. W.B.Saunders, Philadelphia.*

chronological ages demonstrate dramatically different degrees of maturity as evidenced by the appearance of secondary sexual characteristics. In addition, they exhibit changes in the proportion and distribution of subcutaneous fat, and the development of the skeleton and musculature that result in sexually dimorphic body shapes in adulthood.

While each individual has passed through the same chronological time span they have done so at very different rates of maturation.

Secondly, maturation is most often assessed by the identification of "maturity indicators". Such indicators are discrete events or stages recognisable within the continuous changes that occur during the process of maturation. Thus the maturity indicators that identify breast or pubic hair development divide the *continuous* changes that occur into discrete stages.

Thirdly, there is variability of maturation *within* the individual. For instance, while skeletal and secondary sexual maturation are associated they are not correlated so significantly that one can categorically associate a particular stage of sexual maturation with a particular skeletal "age".[2,3] In the closest association, of skeletal age to menarcheal age, it is possible to state that a girl with a skeletal age less than 12 years is unlikely to have experienced menarche and that one with a skeletal age of 15 years is likely to be post-menarcheal. We cannot state with any real degree of confidence that the association of these two maturational processes is closer than that.

Fourthly, within a particular maturational process, such as sexual maturation, it is apparent that different structures, e.g. genitalia and pubic hair, will not necessarily be at precisely the same level of maturity. Thus we have a process of "uneven maturation".

Fifthly, there is clear sexual dimorphism within human growth and maturation such that females tend to be advanced relative to males at any particular chronological age. In Fig. 12.1 for instance, the females are aged exactly 12.75 years and the males are aged 14.75 years, yet their levels of secondary sexual development are similar.

Sixthly, maturation is not related to size except in very general terms; a small individual is likely to be a child and thus less mature than a large individual who is more likely to be an adult. As the ages of the two individuals approach each other so the distinction between size and maturity narrows and disappears such that, within a group of similar maturity there will be a range of sizes and within a group of similar size there will be a range of maturity levels. Thus, when maturation is assessed, size must be controlled for or excluded from the assessment method.

These six considerations, the relationship of maturity to time, the quantification of the continuous process of maturation by using discrete events, the relative independence of different processes of maturation within the individual, the appreciation of uneven maturation, sexual dimorphism, and the lack of a relationship between maturity and size, have governed the development of techniques for the assessment of maturation.

The concept of time

Roy M. Acheson[4] (1921–2003) elegantly described the problem of "time" within the development of skeletal maturity assessment methods.

"Because maturation is distinct from growth it merits a distinct scale of measurement, indeed the whole basis of the medical and scientific interest it attracts is that it does not to proceed at the same rate in the various members of a random group of healthy children. The corollary of this is that the unit of measurement, "the skeletal year", does not have the same meaning for any two healthy children, nor even … does a skeletal year necessarily have the same meaning for two bones in a single healthy child." (Acheson[4] p. 471).

The core problem is the use of an age scale to represent maturity. This fails at the extreme because no particular age can be associated with full maturity, and it fails prior to full maturity because of the lack of a constant relationship between maturity and time both between and within the sexes. Thus, when using the Greulich-Pyle Atlas technique for skeletal maturity[5] one is faced with the final "standards" for males and females which correspond to an "age" of 18 years but which in fact represent full maturity or the maturity to be found in any individual who has achieved total epiphyseal fusion regardless of his or her actual chronological age. The final standard might therefore be better described as an age older than 17 years.

To overcome the problem of an age based method in the assessment of skeletal maturity, Acheson,[6,7] and Tanner and his colleagues,[8–10] developed the "bone specific scoring" techniques in which numerical scores were assigned to each bone (bone score) rather than anage (bone age). Acheson's earlier attempt, which became known as the "Oxford Method" simply gave scores of 1,2,3, etc to each stage. However, this scoring method did not account for the fact that the differences between stages were not equivalent; the "difference" between stage 1 and stage 2 was not necessarily equivalent, in terms of the advancement of maturity, to the difference between stages 2 and 3. Tanner's basic principle was that the development of each single bone, within a selected area, reflected the *single* process of maturation. Ideally, the scores from each bone in a particular area should be the same and the common score would be the individual's maturity. However, such scores would not be the same because of the large gaps between successive events in a single bone. Therefore the scoring process would need to minimize the overall disagreement between different bones. The disagreement is measured by the sum of squares of deviations of bone scores about the mean score, and it is this sum which is minimized. (It is a common statistical procedure to investigate variation about a fixed point, such as the mean, by squaring the positive and negative deviations before taking the square root of the sum and then dividing the sum by the number of deviations. This strategy provides an average deviation without regard to sign (i.e. direction).) In order to

avoid what Tanner described as the "trivial solution" of perfect agreement by giving the same scores to each stage, the scores were constrained on a scale of 0−100, i.e. each bone starts at zero and matures at 100. In essence, each maturity indicator is rated on a maturity scale from zero percent maturity to 100% maturity. Without dwelling on the mathematics, which are given in detail by Tanner in his 1983 publication,[10] the principle is an important one and should be applied to any *new* system of assessing maturity. In addition, the bone-specific scoring approach can be applied to an appropriate sample of radiographs from any population to derive maturity norms.

The principle of scoring maturity indicators was later applied to the assessment of dental maturity by Demirijan, Goldstein and Tanner[11] but, to date, has not been applied to other attempts at maturational assessment such as secondary sexual development. The reason for this apparent neglect may be because we still use the staging system originally developed by Nicholson and Hanley[12] and modified by Tanner and his colleagues in 1962.[9] Only five stages are used within any particular area and these are often difficult to assess accurately. Also secondary sexual development takes place over a relatively short period of time, say between 10 and 17 years in girls, compared to the birth to adulthood temporal basis of skeletal maturity. Thus one is faced with fewer maturity indicators within a short period of time and the application of a scoring technique has seemed inappropriate. However, other aspects of skeletal maturity may lend themselves to a scoring system. Cranial suture closure, for instance, has rarely been investigated as an indicator of maturity in children. Yet this latter technique is important in biological anthropology in which the maturity of skeletal remains is of forensic interest to determine chronological age, and of course, in palaeo-anthropology, in which the maturity of "sub-adult" fossil has a bearing on the interpretation of the morphology of the individual. Meindl and Lovejoy[13] have described a "revised method" for determining skeletal age using the lateral-anterior sutures. They use a scoring system which is the equivalent of Acheson's scoring system for the Oxford method and in so doing repeat the erroneous concept that differences between scores are equivalent, i.e. that the difference between stage 1 and 2 is the same as that between stage 2 and 3. Suture closure is a suitable area for the application of the methods developed by auxologists and would have broad relevance within biological anthropology.

Maturity indicators

The development of the concept of maturity indicators by Wingate Todd,[14] based on the pioneering work of Milo Hellman in 1928,[15] was fundamental in developing methods to accurately assess skeletal maturity. Prior to the identification of maturity indicators, skeletal maturity was assessed by the "number of ossification centers" method in which a count was made, either from the hand and wrist[16,17] or from a skeletal survey of each child,[18] of the number of centers that were present or absent in the total skeleton.

Alternatively planimetry was used to assess the total amount of bony tissue apparent in radiographs.[19–21] The former method failed because of a lack of appreciation of the fact that the order of appearance of ossification centers is largely under genetic control[22] and the latter method because only the carpus was used which, as we now appreciate, is not representative of overall maturity.

I define a maturity indicator as a definable and sequential change in any part or parts of the body that is characteristic of the progression of the body from immaturity to maturity. Skeletal development provides the clearest example of such maturity indicators.

Fig. 12.2 illustrates the maturity indicators for the developing radius used in the atlas and bone specific scoring methods of Greulich and Pyle (GP)[5] and Tanner, Whitehouse and Healy (TW).[9] Both groups examined the development of the radius apparent in radiographs of the left hand and wrist of children from birth to adult maturity. The former group identified 11 indicators while Tanner et al.[9] described eight. It is apparent however that Tanner et al.[9] and Greulich and Pyle[5] concurred in their description of these maturity indicators. Indeed it is extremely important that they did concur. If the two groups of researchers had disagreed in their description of maturity indicators within the same skeletal area, then each group would have been identifying *different* aspects of maturation and would cast doubt on our ability to recognize unequivocal indicators of the process of

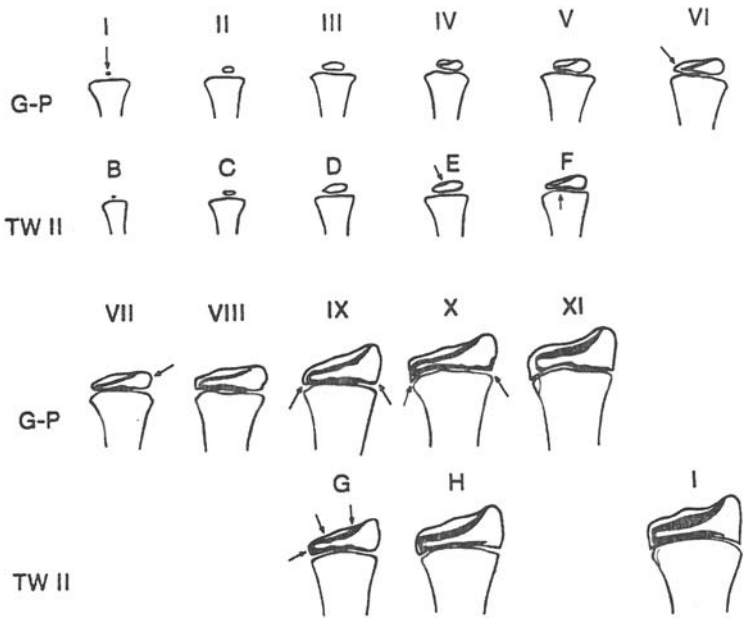

Fig. 12.2
Maturity indicators for the radius as defined by Greulich and Pyle[5] and Tanner and Whitehouse.[10]

maturation. Regardless of the particular maturational process under investigation, the identification of maturity indicators is fundamental to quantifying that process and arriving at measures of individual and population variation.

Maturity indicators must, however, conform to certain pre-requisites if they are to be useful. They must possess the quality of "*universality*" in that they must be present in all normal children of both sexes and they must appear *sequentially*, and in the same sequence, in all children. They must have the ability to *discriminate* between different stages of maturation and reflect a continuous process of maturation through to adult maturity and thus be *complete* in adulthood. As they are to be used as measures of maturation they must be *reliable* both within and between different observers and *validly* reflect the process of maturation.

While such criteria may appear obvious it is possible to find examples of maturity indicators that simply do not conform to these desiderata. For instance, "age at semenarche" was reported in terms of a mean and standard deviation, for a sample of boys from the Transkei region of South Africa who had completed a self-administered questionnaire.[23] The question each boy responded to was, "How old were you when you had your first wet dream (ejaculation)?" One can appreciate that the accuracy of the response to such a question is at best dubious, and indeed the authors maintained that their estimate of mean age at semenarche, "… was crude, and relied on recall of a fairly nebulous isolated event that in most cases is difficult to recall precisely." (Buga, 1996 personal communication). Such estimates ignore the fundamental rationale of maturity indicators and are not constructive to the accurate determination of sexual maturity.

Without maturity indicators we cannot develop methods to assess the process and thus when we search for new methods the "holy grail" of that search is the identification of appropriate indicators of maturity.

Maturational variation

Maturational variation covers two aspects, (1) the variation of maturation *within* a process and (2) the variation of maturation *between* processes. The former aspect may be observed within sexual maturation from the data published by Marshall and Tanner[2,3] on British children. They illustrated variation by investigating the percentage of girls or boys within any particular stage of development of one indicator of maturation when they entered a particular stage of another indicator. For instance, 84% of girls were in at least stage 2 of breast development when they entered stage 2 of pubic hair development. In other words they did not enter pubertal maturation in both breast and pubic hair development simultaneously. Breast development for the vast majority was the first stage of puberty followed by pubic hair development. Similarly, 39% of girls were already adult for breast development when they became adult for pubic hair development.

A similar pattern of variation was observed in males with 99% of boys starting genitalia development prior to pubic hair development. This variation is critical in that it requires any modification of the method to allow for intra-individual variation. Within clinical situations, for instance, the difficulties in accurately rating the various stages of breast, genitalia, or pubic hair development within the Tanner five-point classification have led to the combination of the stages into a three or four-point "pubertal" staging technique. In the three-point technique, stage P1 represents the pre-pubertal state (B1/G1; PH1) and stage P3 the post-pubertal state (B5/G5; PH5). All indicators of maturational change between these two extremes have been combined into the P2 stage. Thus variations within individuals between the different aspects of secondary sexual development are impossible to quantify and, in terms of research to investigate variability in maturation, the pubertal staging technique loses significant sensitivity. The variation of maturation between different aspects of maturity presents difficulties in implying a general maturational level to the individual. For instance, entry into the early stages of puberty is apparently not associated with any particular level of skeletal maturity except in the broadest sense. The only real exception to this rule, with regard to skeletal and sexual maturation, is menarcheal age in which skeletal age and chronological age are associated at a level of 0.35 and in which menarche tends to occur at a skeletal age of 12.5−14.0 "years" regardless of chronological age.

It may appear strange that these two maturational processes do not appear to be more closely related. As one would expect there is evidence that skeletal maturity is related to changing levels of growth hormones, such as insulin-like growth factor 1 (IGF-1) during puberty.[24] Sex steroids also increase dramatically during puberty and the action of these hormones (GH, IGH-1, testosterone, estrogen) clearly affects the mineralization of the skeleton.[25] It may be that our ability to assess secondary sexual development is simply not sophisticated enough to accurately reflect the hormonal changes that cause the morphological changes associated with puberty. Menarche, on the other hand, is usually an obvious and accurately timed maturational event that therefore can be statistically associated with skeletal maturity.

Maturity indicators derived from mathematical functions that describe the growth curve might be far more useful than morphological indicators because much closer associations are evident between markers of somatic growth and skeletal maturity. For instance, skeletal and chronological ages are known to be uncorrelated at 95% of mature height and therefore skeletal age is more or less fixed at 95% mature height regardless of chronological age. Thus function parameters that have a real biological meaning have the potential to be appropriate maturity indicators. The problem is that most existing functions have resulted from attempts to smooth the growth curve or to reduce data rather than to understand the biology of growth. For example, the family of models proposed by Preece and Baines[26] [see Chapter 3] resulted from attempts to model the total growth curve with

the fewest parameters. Previous attempts by Bock et al.[27] had resulted in double or triple logistic curves involving nine or more parameters for which clear biological meanings were not apparent. Preece and Baines[26] were able to model using just five parameters to which they were also able to assign biological meaning, e.g. age and height at peak height velocity. That "biological" meaning resulted from the fact that high correlations were apparent between the function parameter and the maturational event. For example, in Model 1, θ correlated with age at PHV at a 0.99 level for boys and a 0.97 level for girls, $H\theta$ at a 0.99 level with height at PHV in both males and females. But one needs to be cautious about implying direct associations between the function parameters and the maturational events; the rate constants S_0 and S_1 for instance, correlated most strongly with velocity at take-off and velocity at PHV but only at the 0.50 and 0.55 levels. However, the possibility of using function parameters as maturity indicators is an attractive prospect particularly as mathematical modeling moves us closer to a more accurate depiction of the pattern of human growth.

Sexual dimorphism

Ideally any method that assesses maturity should be able to assess the same process of maturation in both males and females. That criterion is true of skeletal and dental maturity assessment methods and also of methods that might be developed from mathematical models of the pattern of human growth. It is not, of course, true of all aspects of secondary sexual development although the gender specific assessment methods have a great deal in common. In the former methods sexual dimorphism is accounted for by having gender specific scores for each bone or tooth and in the latter by identifying equivalent functional processes in the different sexes. However, the interpretation of maturation, or the meaning of the attainment of a particular level of maturity, may be different within the sexes. For instance, it could be argued that spermarche and menarche are equivalent stages of maturation in males and females yet their position within the pattern of growth is quite different and thus their association with other aspects of maturation also differs. Extensive data on menarche demonstrates that it occurs following peak height velocity and toward the latter part of secondary sexual development, i.e. in breast stage 3, 4, or 5. Relatively sparse data on spermarche identifies its occurrence at approximately 14 years in boys, which would be in the early or middle part of the adolescent growth spurt and thus indicative of an earlier stage of pubertal maturation.

Maturity and size

The fact that a large individual is likely to be older and thus more mature than a small individual was emphasized earlier in this review. This might indicate that size should in some way be included in a consideration of maturation. Indeed the early methods of

skeletal maturity assessment by planimetry used precisely that reasoning. It is now clearly recognized that, except in very general terms, size does not play a part in the assessment of maturation. Size does however enter assessment as a maturity indicator as a ratio measure. For example, the maturity indicator for stage D in the radius of the TWII system is the fact that the epiphysis is "half or more" the width of the metaphysis, i.e. the size is relative to another structure within the same area. However, except for such a ratio situation, the only maturity assessment method that uses a quantitative indicator of maturity is testicular volume, 4 mL represents the initiation of pubertal development and 12 mL mid-puberty. This is not to say that there is no variation in testicular volume. Like all aspects of growth and development, variability is an inherent aspect of testicular growth. Clinicians, however, use the above measures as indicators of normal testicular growth and of the initial and middle stages of pubertal development.

Methods of assessment

Maturation is assessed using a combination of processes and events. Maturational "processes" include secondary sexual development, dental development and skeletal development. Maturational "events" include those aspects of maturation that occur once and provide an unambiguous signal that the individual has reached a particular level of maturity. For example, the exact age at which menarche (the first menstrual period) is experienced in girls or the exact the age of peak height velocity during the adolescent growth spurt.

Secondary sexual development

Secondary sexual development is assessed using maturity indicators that provide discrete stages of development within the continuous process of maturation. The most widely accepted assessment scale is described as the Tanner Scale or the Tanner Staging Technique. It was developed by Tanner[28] and was based on the work of Reynolds and Wines[29] and Nicholson and Hanley.[12] Tanner[28] divided the processes of breast development in girls, genitalia development in boys, and pubic hair development in both sexes into five stages and axillary hair development in both sexes into three stages. The usual terminology is to describe breast development in stages B1− B5, genitalia development in stages G1-G5, pubic hair development in stages PH1-PH5 and axillary hair development in stages Al-A3.

Breast development

Stage 1: Pre-adolescent: elevation of papilla only.

Stage 2: Breast bud stage: elevation of breast and papilla as small mound. Enlargement of areolar diameter.

Stage 3: Further enlargement and elevation of breast and areola, with no separation of their contours.

Stage 4: Projection of areola and papilla to form a secondary mound above the level of the breast.

Stage 5: Mature stage: projection of papilla only, due to recession of the areola to the general contour of the breast. (Fig. 12.3)

Genitalia development

Stage 1: Pre-adolescent: testes, scrotum and penis are of about the same size and proportion as in early childhood.

Stage 2: Enlargement of scrotum and testes: the skin of the scrotum reddens and changes in texture. There is little or no enlargement of penis at this stage.

Stage 3: Enlargement of penis: this occurs first mainly in length. Further growth of testes and scrotum.

Stage 4: Increased size of the penis with growth in breadth and development of glans. Further enlargement of testes and scrotum; increased darkening of scrotal skin.

Stage 5: Genitalia adult in size and shape. (Fig. 12.4)

Pubic hair development

Stage 1: Pre-adolescent: the vellus over the pubes is not further developed than that over the abdominal wall, i.e. no pubic hair.

Stage 2: Sparse growth of long, slightly pigmented downy hair, straight or only slightly curled, appearing chiefly at the base of the penis or along the labia.

Stage 3: Considerably darker, coarser and more curled. The hair spreads sparsely over the junction of the pubes.

Stage 4: hair now resembles adult in type, but the area covered by it is still considerably smaller than in the adult. No spread to the medial surface of the thighs.

Stage 5: Adult in quantity and type with distribution of the horizontal or classically feminine pattern. Spread to the medial surface of the thighs but not up the linea alba or elsewhere above the base of the inverse triangle. (Fig. 12.5)

Clinical evaluations

The assessment of secondary sexual development is a standard clinical procedure and at such times the full Tanner Scale is used. There are some practical problems with the

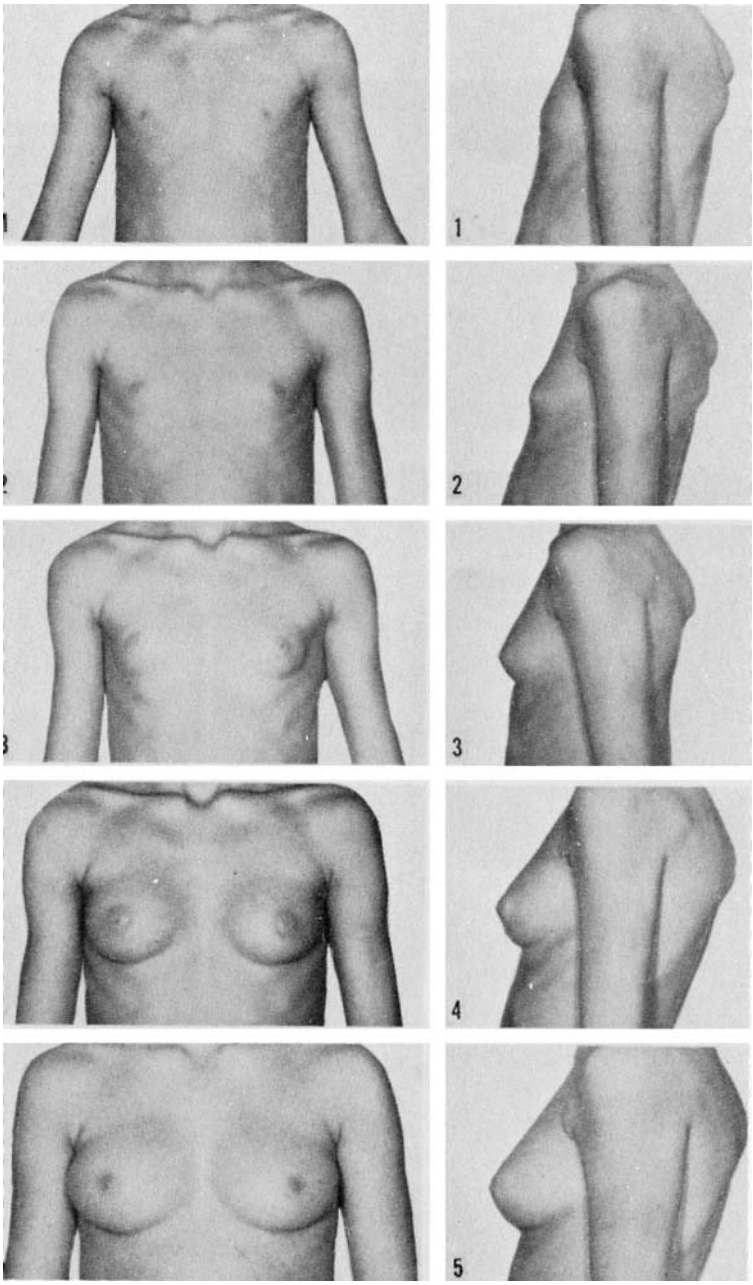

Fig. 12.3
Breast standards from the Tanner method. *From Tanner JM.* Growth at Adolescence. *2nd ed. Oxford: Blackwell Scientific Publications;1962.*

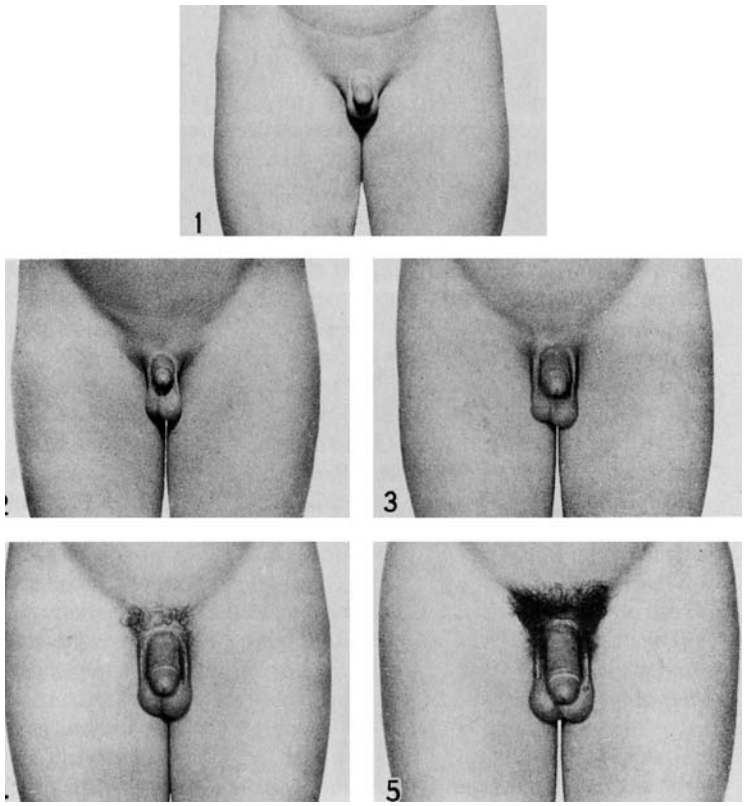

Fig. 12.4
Genitalia standards from the Tanner method. *From Tanner JM.* Growth at Adolescence. *2nd ed. Oxford: Blackwell Scientific Publications;1962.*

Tanner stages, however, in that the unequivocal observation of each stage is often dependent on having longitudinal observations. In most situations, outside the clinical setting, the observations are cross-sectional. This practical difficulty has led to the amalgamation of some of the stages to create pubertal stages. These pubertal stages are either on a three or four-point scale and combine breast/genitalia development with pubic hair development.[30,31] Assessing breast/genitalia development with pubic hair development is obviously much easier than assessing these maturity indicators separately, but inevitably leads to a lack of sensitivity in the interpretation of the timing and duration of the different stages of pubertal development. Indeed the intrasubject variation in the synchronous appearance of pubic hair and breast/genitalia stages, illustrated in British children by Marshall and Tanner,[2,3] suggests that it may be misleading to expect stage synchronization in as many as 50% of normal children.

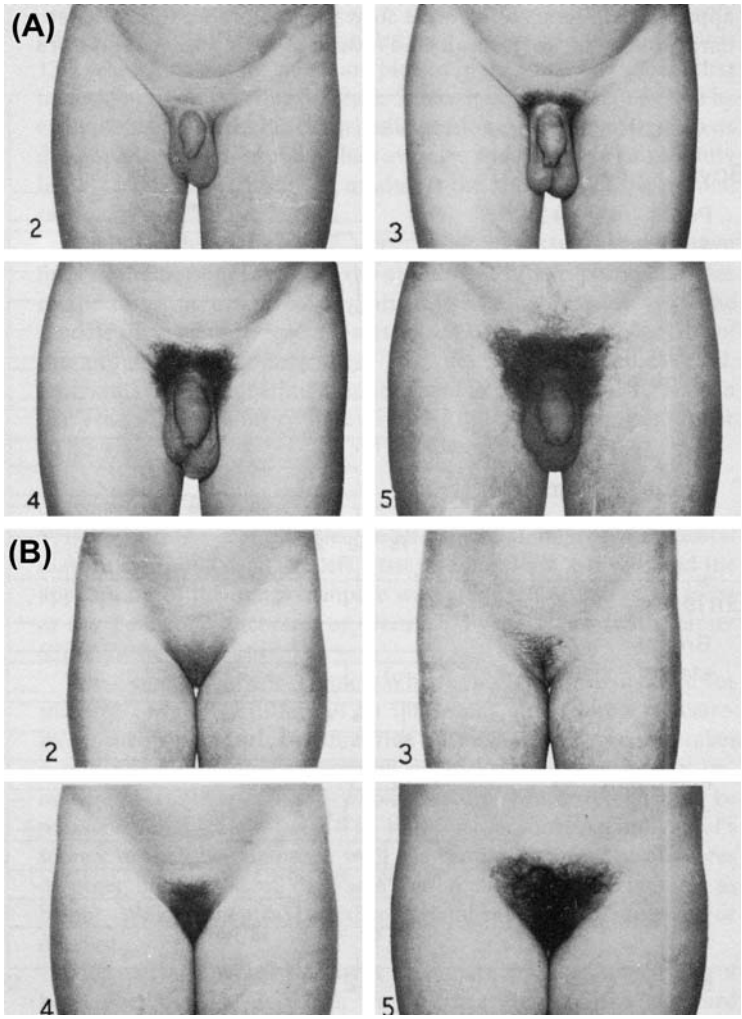

Fig. 12.5
Pubic hair standards from the Tanner method. *From Tanner JM.* Growth at Adolescence. *2nd ed. Oxford: Blackwell Scientific Publications;1962.*

Self-assessment of pubertal status

The assessment of secondary sexual characteristics is, to some extent, an invasive procedure in that it invades the privacy of the child or adolescent involved. Thus such assessments on normal children who participate in growth studies, as opposed to those being clinically assessed, are problematical from both ethical and subject compliance viewpoints. In order to overcome this problem the procedure of "self-assessment" has been developed and validated in a number of studies.

The self-assessment procedure requires the child to enter a well-lit cubicle or other area of privacy in which are provided pictorial representations of the Tanner scales and suitably positioned mirrors on the wall(s). The pictures may be either in photographic or line drawing styles as long as the contents are clear. To each picture of each stage is appended an explanation, in the language of the participant, of what the stage represents. The participant is instructed to remove whatever clothing is necessary in order for them to be able to properly observe their pubic hair/genitalia or pubic hair/breast development in the mirrors. The participant then marks on a separate sheet their stage of development and seals that sheet within an envelope on which is marked the study identity number of the participant. The envelope is either left in the cubicle or handed to the observer on leaving the cubicle.

The results of validation studies vary greatly depending upon the age of the participants (e.g. early or late adolescence),[32] gender,[32,33] the setting in which assessments are performed (e.g. school or clinic),[34,35] ethnicity,[36] and whether they are a distinct diagnostic group such as cystic fibrosis[37] or anorexia nervosa[38] or socially-disadvantaged.[39] Younger less developed children tend to overestimate their development and older more developed children tend to underestimate. Boys have been found to overestimate their development while girls have been more consistent with expert assessment.[33] The amount of attention given to explaining the required procedure appears to be of major importance. Thus excellent rating agreement between physicians and adolescents have been found in clinical settings, with kappa coefficients between 0.66 and 0.91,[35,40,41] but rather less agreement in school settings (kappa = 0.35 − 0.42; correlations = 0.25 − 0.52).[34,35] Improved agreement in clinical settings probably reflects the more controlled environment of a physician's surgery as opposed to a school. The main reason for low correlations and thus poor validity in any setting with any group of participants is likely to be centered on the amount of explanation that is provided to the child. When the participant has been the subject of a clinical trial, and the scientist/clinician has spent considerable time and effort ensuring that the child is completely apprised of what he/she has to do, then validity is high. Less effort in explaining procedures leads to lower validity.

The procedure that should be adopted is that the observer should explain the procedure thoroughly to the participant using appropriate (non-scientific) language and invite questions to ensure that the participant fully understands the procedure. Only when the observer is sure that understanding is total should the child be allowed to follow the procedure. Randomized reliability assessments by the observer would, of course, be ideal but would also be ethically difficult to substantiate.

Dental development

Dental development is best assessed by taking panoramic radiographs of the mandible and maxilla and scoring the stages of formation and calcification of each tooth using the method developed by Demirjian, Goldstein and Tanner[11] and Demirjian and Goldstein.[42] Scores are assigned to the stages of development of the seven mandibular teeth on the left side (there are no significant between-side differences) and these lead to a dental maturity score comparable to the skeletal maturity scores resulting from the Tanner-Whitehouse (TW) skeletal maturity technique described below. This score can be translated into the dental age. A similar system is available for sets of four teeth, seen on apical radiographs, notably M 1, M2, PM1, PM2 or alternatively I1, M2, PM1, PM2.

Concern over the exposure of normal children to radiation has resulted in tooth emergence as the most commonly used method to obtain estimates of dental maturity. The emergence of the teeth above the level of the gum is recorded either by oral inspection or in a dental impression. Most observers have considered that a tooth has emerged if any part has pierced the gum, but some have used the criterion of the tooth being halfway between gum and final position.[43] Three types of standards have been developed that give either the number of teeth emerged at specific ages, or the average age when 1, 2, 3, etc. teeth have emerged, or the median age in a population for the emergence of a specific tooth or pair of teeth. The latter technique is considered the best for permanent teeth because of the individual variation in the order of emergence of each tooth pair.[43]

Skeletal development

While a number of techniques exist to assess skeletal maturity, assessment procedures have been dominated by two different approaches to the problem; the “atlas” technique of Greulich and Pyle[5] and the Tanner-Whitehouse “bone-specific scoring” technique.[10] Both use the left hand and wrist to estimate a skeletal age or bone age yet they are different both in concept and in method. Greulich-Pyle bone ages are most commonly assessed by comparing a radiograph to a series of standard radiographs photographically reproduced in the atlas. The chronological age assigned to the standard most closely approximating the radiograph is the bone age of the subject. In practice a more precise estimate of bone age may be obtained by assessing each bone in the hand and wrist separately, but this is rarely done. Thus, there are errors in most Greulich-Pyle estimations because the dysmaturity present in the hand and wrist is not acknowledged. The system is based on subjects from Cleveland, Ohio, who were assessed during the 1920s and 1930s. The Tanner-Whitehouse system requires 20 bones of the hand and wrist to be assessed individually and a score to be assigned to each. The summation of the scores results in a bone maturity score which is equivalent to a particular bone age. This technique originally used subjects from a variety

of studies conducted in the south of England during the 1950s and 1960s. Although the latter is more recent, the effect of positive secular trends and population differences in average maturity status means that estimates of skeletal age based on either technique must be viewed with some degree of caution although later editions of the Tanner-Whitehouse method (TW3) have corrected for secular trends by using an updated source sample of European children from the 1980s and 1990s.[44] However, the statistical rationale of the bone-specific scoring technique can be applied to any series of radiographs from a representative sample of a population. In contrast to the atlas technique it is thus possible to develop specific national references for the assessment of skeletal maturity using a bone-specific approach which would result in a more sensitive clinical appraisal.

Age at menarche

Age at menarche is usually obtained in one of three ways; status quo, retrospectively, or prospectively. Status quo techniques require the girls to respond to the question, "Do you have menstrual cycles ("periods")?" The resulting data on a sample of girls will produce a classical dose response sigmoid curve that may be used to graphically define an average age at menarche. More commonly the data are analyzed using logit or probit analysis to determine the mean or median age at menarche and the parameters of the distribution such as the standard error of the mean or the standard deviation. Retrospective techniques require the participants to respond to the question, "When did you have your first period?" Most adolescents can remember to within a month, and some to the day, when this event occurred. Others may be prompted to remember by reference to whether the event occurred during summer or winter, whether the girl was at school or on holiday, and so on. One interesting result of such retrospective analyses is that there appears to be a negative association between the age of the women being asked and the age at which they report menarche – the older the women the younger they believe they were. Such results have been found in both developed and developing countries and cast a seed of doubt about the reliability of retrospective methods beyond the teenage and early adult years. Prospective methods are normally only used in longitudinal monitoring situations such as repeated clinic visits or longitudinal research studies. This method requires the teenager to be seen at regular intervals (usually every 3 months) and to be asked on each occasion whether or not she has started her periods. As soon as the response is positive an actual date on which menarche occurred can be easily obtained.

There is little doubt that the prospective method is the most accurate in estimating menarcheal age but it has the disadvantage of requiring repeated contact with the subjects. That is seldom possible except in clinical situations and it is thus more likely that status quo and retrospective methods are the technique of choice. Status quo techniques that rely on logit or probit analysis require large sample sizes because the analysis requires the data

to be grouped according to age classes. With few subjects broader age ranges are required such as whole or half years with a consequent loss of precision in the mean or median value. Retrospective methods result in parametric descriptive statistics but have the problem of the accuracy of recalled ages at this particular event.

Secondary sexual events in boys

While status quo, prospective and retrospective methods may easily obtain age at menarche, assessments of secondary sexual development in boys are complicated by the lack of a similar clearly discernible maturational event. Attempts to obtain information on the age at which the voice breaks, or on spermarche, are complicated by the time taken for the voice to be consistently in a lower register, and the logistical complications involved in the assessment of spermarche. Testicular volume, using the Prader orchidometer,[45] is commonly the only measure of male secondary sexual development outside the rating scales previously mentioned, though other measurement techniques have been described to estimate testicular volume.[46]

The detection of spermatozoa in the urine has been proposed as a quick, non-invasive method to assess the functional state of the maturing gonad and may be useful as a screening technique in population studies.[47–52] Its use, however, may be limited because longitudinal[51,53] and cross-sectional[50] studies have shown that spermaturia is a discontinuous phenomenon.

Hormonal maturity indicators

Blood analysis of the third National Health and Nutrition Examination Survey (NHANES III) has led to the development of threshold values for relevant blood hormones that signal the start of puberty in boys[54] and girls[55] aged 6–11.99 years. LH, Inhibin B and both sexes and with the addition of testosterone (T) in boys, were compared to traditional visual assessments of pubertal development.

In boys and girls mean hormone levels progressively increased with age. In boys hormones were consistent with pubertal onset (Tanner stage 2), except for T and G2. Inhibin B and LH levels increased significantly by genital stage after adjusting for age and race/ethnicity, while LH and T concentrations increased significantly across pubic hair stages. In girls LH levels progressively increased with pubertal stage. Inhibin B levels increased gradually from B1 to B2 then more sharply to peak at B3, followed by a plateau at subsequent stages. Inhibin B and LH were consistent with pubertal onset (B2). Despite these promising results the misclassification rate for hormonal status compared to puberty exam for boys was in the order of 13%–16% across all three hormones and for girls was approximately 25% for both LH and Inhibin B; 13%–16% of boys and 25% of girls

would be classified as being pubertal when in fact they were pre-pubertal. It was thus concluded that these misclassification levels are too high for these hormones to be useful in isolation to indicate the initiation of puberty but were perhaps beneficial in combination with other clinical indicators.[54,55]

Landmarks on the growth curve

The identification of landmarks on the human growth curve that can be used for comparison between individuals or groups started with age at peak height velocity. This is the most distinctive feature of the velocity curve during adolescent growth and may be determined in individual longitudinal data as a change in acceleration from positive to negative values. Use of other landmarks on the curve, such as age at take-off and at the cessation of growth, and the magnitude of height or weight velocity at these ages, did not become prevalent until the implementation of mathematical curve-fitting techniques became possible using personal-computer-based software. Initial curve-fitting techniques used only part of the growth curve (e.g. from birth to the start of adolescence) or involved the addition of different functions. The major problem with these early techniques, apart from their mathematical complexity and biological interpretation, was their relative inability to cover the transition between developmental periods such as preadolescence to adolescence. This was solved to a certain extent by the development of single curves that described growth from birth through to adulthood.[26,27] However, long-term parametric models have the advantage that the researchers pre-select the shape of the resulting growth curve. The choice of the model necessitates the acceptance of its form as being representative of the pattern of growth. Individuals or samples departing from the standard pattern of growth in height or weight would not be fitted well by any of these parametric functions. Estimates of landmarks on the growth curve are difficult to determine. Tanner and Davies,[56] for instance, when developing the clinical longitudinal standards for American children, relied on empirically derived values for the magnitude of peak velocity because "parametric curves … are insufficiently flexible to accommodate the full rise of the observed curves" during adolescence[56] (p. 328). The widely used Preece-Baines curve,[26] for example, is known to underestimate the peak velocity.

Non-parametric models, such as the smoothing spline function[57] and kernel estimation,[58,59] have been proposed to overcome the problems inherent in pre-selection of a pattern of growth. Non-parametric techniques are usually short-term functions that smooth adjacent data points rather than fit a function to data from birth to adulthood. They have been useful in demonstrating the sensitivity of growth analysis using acceleration[58,59] but cannot result in mathematically derived values for adolescent landmarks such as the age and magnitude of peak velocity. Such landmarks, if taken from curves that have been smoothed using non-parametric techniques, may be more accurately determined than if

derived from a parametric function. However, that accuracy is dependent on the frequency of data points during the period of adolescence. The inability of pre-selected parametric functions to fit abnormal growth and the retrospective nature of growth assessment of non-parametric methods make these techniques useful as research tools but not for diagnosis and monitoring the value of treatment.

Summary

The assessment of maturation depends on the identification of a series of maturity indicators that characterize the transition from immaturity to maturity in all children. These maturity indicators must be universal, sequential, discriminant, reliable, valid and complete in their characterization of maturation. The study and assessment of maturity has been confined to processes and events; the processes of skeletal, dental and sexual maturity and the events of menarche, spermarche, changes in sex hormone levels and inflection on the growth curve such as peak height velocity.

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Internet sources

A variety of internet sources of information on maturity assessment are apparent when using a major search engine such as Google. However, the reader is warned that searches that include the term "sexual" as in "secondary sexual development" will inevitably link to web sites featuring "adult content".

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CHAPTER 13

Modeling growth curves for epidemiology

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Finding the curve

The key guiding principle of all growth curve modeling, no matter how complex the data or analytical approach, is that you are fitting a curve (or curves) through serial measurements on an individual (or individuals). While Scammon produced a curve describing the growth of De Montbeillard's son by connecting the dots (i.e., measurements) together by hand,[1] scientists are very rarely, if ever, faced with a single child with six-monthly, highly accurate measurements. Even if they were, developing a mathematical model that describes the growth curve would be beneficial, not least because it would allow exact estimation of traits like peak height velocity (PHV). As others have already done,[2] we could produce a model of the growth of De Montbeillard's son by regressing the length/height data on some appropriate function of age. This is the simplest form of a growth model and (as with any growth curve analysis) our task would be in "finding the curve" that best explains the pattern observed in the data. A simple age function might not have the required flexibility and would result in a large amount of model error (i.e., distances between the data points and the curve). Conversely, an age function that is too complex and flexible might produce a wiggly curve that suffers from bias by trying to pass exactly through every data point. The degree of smoothing to perform should be chosen with the aim to minimize the error, but not to the extent that you introduce bias. As a rule of thumb, the average error in a model should be approximately the same as the measurement error of the dimension being considered. This would mean that any model error largely reflects measurement error. Inspecting the plot of a curve against the data will reveal all and should be a key step in any analysis.

Auxological models

There are an infinite number of models or age functions for researchers to pick from to fit a curve to their data. Fortunately, one of the main themes of auxological research in the 20th century was developing models specifically for human physical growth. These have

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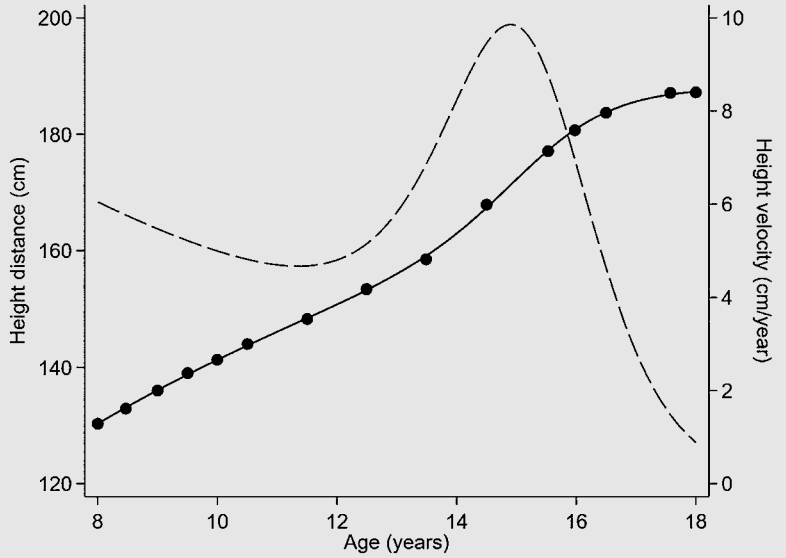
been summarized and discussed in detail by Hauspie and Molinari in a book chapter which serves as an excellent starting point for anyone wanting to model human physical growth curves.[3] The open-access Ph.D. thesis of Richard Silverwood also includes a great review of the models that have been most influential.[4] These auxological models are also known as structural models because they postulate that the growth curve has a specific functional form (e.g., height approaches an asymptote or horizontal line during late adolescence) and often include parameters that have some biological interpretation.

As an example, the formula of a model published by Michael Preece and Jan Baines in 1978 for linear growth after infancy is shown in Box 13.1.[5] The astute reader will notice that this is a non-linear model because there are terms that are neither a constant (β_0) nor

Box 13.1 The Preece-Baines model

$$y = h_1 - \frac{2(h_1 - h_\theta)}{e^{s_0(a-\theta)} + e^{s_1(a-\theta)}} + e$$

Where, y is height, a is decimal age, h_1 is an estimate that approximates adulthood height, θ is an estimate that approximates age at PHV, h_θ is an estimate that approximates height at PHV, s_0 and s_1 are growth rate constants related to pre-pubertal and post-pubertal velocities, and e is the error.



the product of a parameter and an independent variable ($\beta_1 x$). Other functions developed specifically for human growth do, however, follow this format.[6,7] Auxological models can thus be sub-divided into linear and non-linear models. The estimation of non-linear models may be more computationally intensive, but all core statistical programmes have this capability. Box 13.1 also shows the distance and velocity curves produced by fitting the non-linear Preece-Baines model to 15 serial measurements on a healthy boy. The distance curve is clearly providing an excellent fit to the data (which clearly has little measurement error) and the velocity curve is archetypical. Further, the parameters for timing and magnitude of PHV (15.2 years and 174.5 cm) approximate the estimates (14.9 years and 171.3 cm) computed using updated solutions published in 2017 by Sayers et al.[8]

For most skeletal dimensions (e.g., leg length and bi-acromial width), and for most periods of growth, there exists an auxological model that will work well, if not better than any known alternative function. Understanding the history of growth curve modeling, and the different functions that have been developed and compared over the years, is therefore of paramount importance (not least to avoid reinventing the wheel). Some of the auxological models have been shown to accurately describe body weight[9,10] although this measurement, and soft tissue measurements such as fat mass, are less strongly regulated than skeletal growth and investigation using more flexible modeling approaches maybe warranted. This is particularly true for body mass index (BMI) and other indices which demonstrate complex and highly variable patterns of change over age.[11,12]

Non-auxological models

When no auxological model exists for the data under consideration, researchers normally employ some generic method of curve fitting that is not specific to human growth research. Gasser et al. provide a good review of some of the approaches available.[13] These non-auxological models are also called non-structural models because they do not postulate that the growth curve has a specific functional form. They are just a way of smoothing data and it is easy to keep adding more and more flexibility to the curve, making it particularly important to choose the right degree of smoothing to avoid bias.

Polynomials are the simplest and perhaps most common way of testing for, and describing, a curvilinear relationship. Their generic form is given by:

$$y = \beta_0 + \beta_1 x + \beta_2 x^2 + \ldots + \beta_p x^p + e$$

A model including age (x) and age-squared (x^2) is a quadratic or second-degree polynomial. If a more complex curve is required then an age-cubed term (x^3) could be added, resulting in a cubic or third-degree polynomial model. For this model, the velocity curve (i.e., first derivative) follows a quadratic form, the acceleration curve (i.e., second derivative) is linear, there is one inflection point (where acceleration changes from positive

to negative, or vice versa), and there may be a maximum of two critical points (where velocity equals zero due to a peak or trough). If these characteristics are not realistic for the growth process being considered, it is easy to see how the researcher could keep expanding the model to a fourth, fifth, sixth, etc degree polynomial function. The problem, however, is that polynomials rapidly become unstable as more terms are added and are notorious for spurious oscillations. A general recommendation is to only use polynomials for simple curves and not to go beyond a quartic or fourth-degree specification.

Fractional polynomials provide a more flexible way of modeling growth curves.[14,15] Their generic form is given by:

$$y = \beta_0 + \beta_1 x^{p_1} + \beta_2 x^{p_2} + \ldots + \beta_m x^{p_m} + e$$

This equation is very similar to that for conventional polynomials, the difference being that the powers with which to raise each age term are not user-specified but are selected from an automated procedure comparing all possible options. The powers p_1−p_m are chosen from a set normally comprising −2, −1, −0.5, 0, 0.5, 1, 2, and 3, where 0 means log. For an understanding of how powers are treated when repeated (e.g., $p_1 = 0.5,\ p_2 = 0.5$), and other more nuanced aspects of this approach, the reader is directed to Royston & Sauerbrei's book.[14] For a two-degree model (i.e., two age terms), 36 different combinations of powers are tested. And for a three-degree model, 120 different combinations of powers are tested. The user is then presented with the best function, based on the lowest deviance (i.e., −2 Log Likelihood), to describe their data. The flexibility of this approach and its automation (for example using the fp command in Stata) makes it an attractive option for modeling growth curves. Again, however, a general recommendation is to not go beyond a three-degree or perhaps four-degree specification. The paper by Wen et al. provides a good example of how high-order fractional polynomials fail to accurately describe BMI trajectories from one week to 18 years of age.[16] One could argue that it might better to model different parts (e.g., 0−3 years and 3−18 years) of the BMI curve separately. Alternatively, in this type of scenario, a different approach is needed.

Splines are commonly used to smooth data. There are numerous types, the simplest being linear or piecewise splines. Briefly, regression with linear splines produces a series of straight lines, covering different sections of the age range, that are connected at transition points known as knots.[17] This approach has become popular in epidemiology because the parameters are meaningful (i.e., each slope represents the rate of change during an age period) but is not considered further because it does not produce a smoothed curve. Restricted or natural cubic splines, on the other hand, are a method widely used to produce complex smoothed curves, and have the general form:

$$y = \beta_0 + \beta_1 S_1 + \beta_2 S_2 + \ldots + \beta_n S_n + e$$

The S_{1-n} are restricted cubic spline terms of age. They are constructed before fitting the regression model, using an appropriate spline basis function. The two main options are the B-splines basis and the truncated-splines basis.[18,19] All statistical programs have commands that will compute the restricted cubic spline terms for you, without the need for advanced maths and programming knowledge. The user normally specifies the number of knots, with more knots equaling more flexibility. N knots will produce N−1 restricted cubic spline terms, the first of which is equal to age ($S_1 = x$). In most instances, between 3 and 7 knots provide the flexibility required for complex growth curves.[20] The location of the knots is less important and a common strategy (which is often implemented by default) is to place the knots at fixed quantiles of the age distribution, such as those recommended by Harrell.[20] An important consideration is that, with restricted cubic splines, the resulting growth curve will be linear before the first knot and linear after the last knot. This is one benefit of this approach over normal non-restricted cubic spline functions, a second being that restricted cubic splines are more parsimonious (i.e., have fewer terms for the same degree of flexibility).

Individual or sample-average curves

Fitting a curve for just one individual not only requires substantive knowledge of how children grow and develop, but also an understanding of the different auxological and non-auxological models that are available. Multiple models (or at least variants of a model) are normally tested and compared before an appropriate function can be chosen. With serial data on one individual this is not too challenging, but with a sample you presumedly want a single model that works for everyone. Once this is found, human biologists used to have to painstakingly fit a separate regression for each child and extract any parameters or traits of interest for use in secondary analyses. A sample average curve, for example, would be computed using the mean values for each of the parameters. Fortunately, strategies are now available to fit growth curves for an entire sample in one model.

Multilevel growth curve models

Multilevel models were largely developed in the 1980's in education research to investigate how academic performance outcomes were determined by the interplay between individual-level and "contextual" school-level variables.[21,22] Today, multilevel models are a common analytical technique in a wide-range of disciplines in which hierarchical data are encountered. Longitudinal growth data are one such example because serial anthropometric measurements (level 1) are clustered within children (level 2).

Key principles

Multilevel models efficiently handle longitudinal growth data on a sample of children by estimating (1) sample average parameters called "fixed effects" that govern the average growth curve and (2) corresponding child specific parameters called "random effects" that are individual departures from the fixed effects. The fixed and random effects together (i.e., mixed effects) describe the growth of every child in a sample. The formula for a random intercept and linear slope multilevel model is provided in Box 13.2, along with an illustration of how the parameters describe the trajectory for a theoretical child with five serial measurements.

In conventional regression models, there is one type of variance, which is a summary of the differences between the observations and the fitted curve (i.e., the residuals). With longitudinal data, these residuals will be autocorrelated because any given child's serial measurements will consistently be above or below the fitted curve across all or large parts of the age scale. Multilevel models resolve this problem by incorporating estimated random effects that allow each child to have their own curve. The values of the random effects are called level 2 residuals (because they are child specific) and they capture the level 2 or between-individual variance. The differences between each child's observations and their fitted curves are now called level 1 residuals (because they are occasion specific) and they capture the level 1 or within-individual variance.

The variance in a typical multilevel growth curve model is therefore partitioned across two levels. In our example in Box 13.2, we could get an idea of the amount of variation at level 1 by taking the square root of σ_e^2 to get the estimated standard deviation. Similarly, we could investigate the amount of variation in the random intercepts and slopes at level 2 by taking the square roots of $\sigma_{\mu 0}^2$ and $\sigma_{\mu 1}^2$. The $\sigma_{\mu 01}$ term describes the covariance between the random intercepts and slopes and to aid interpretation this can be expressed as a correlation using the formula:

$$\sigma_{\mu 01} / \sqrt{\sigma_{\mu 1}^2 * \sigma_{\mu 0}^2}$$

A covariance or correlation greater than zero means that individuals with a random intercept greater than zero (i.e., the sample average) will tend to have a random slope greater than zero (i.e., the sample average). Note that if β_1 is negative, a positive covariance or correlation could indicate that individuals with higher intercepts have flatter (less negative) than average slopes. A covariance or correlation greater than zero also implies that the between-individual variance will increase after $x = 0$ (because the individual trajectories will fan out). Conversely, a covariance or correlation less than zero implies that the between-individual variance will decrease for at least some time after $x = 0$ (because the individual trajectories will fan in, before possibly crossing over and fanning

Box 13.2 A multilevel model with random intercept and slope

$$y_{ij} = \beta_{0ij} + \beta_{1j}x_{ij}$$

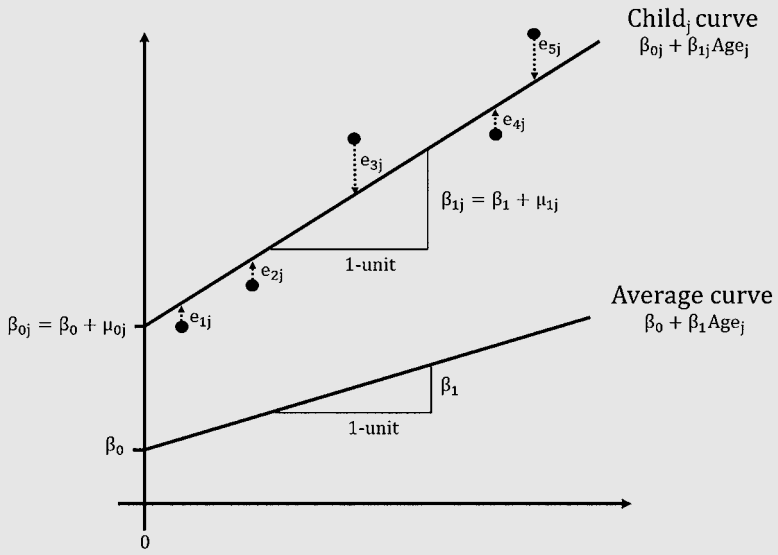
$$\beta_{0ij} = \beta_0 + \mu_{0j} + e_{ij}$$

$$\beta_{1j} = \beta_1 + \mu_{1j}$$

$$\begin{bmatrix} \mu_{0j} \\ \mu_{1j} \end{bmatrix} \sim N(0, \Omega_\mu): \quad \Omega_\mu = \begin{bmatrix} \sigma^2_{\mu 0} & \\ \sigma_{\mu 01} & \sigma^2_{\mu 1} \end{bmatrix}$$

$$[e_{ij}] \sim N(0, \Omega_e): \quad \Omega_e = [\sigma^2_e]$$

Where, y_{ij} is the size at age i of child j and x_{ij} is the corresponding age. β_{0j} and β_{1j} are individual-specific coefficients, comprising fixed effects (β_o and β_1) that describe the average trajectory and random effects (u_{0j} are u_{1j}) that capture individual departures from average trajectory. The u_{0j} and u_{1j} are assumed to follow a joint normal distribution with zero means, variances σ^2_{u0} and σ^2_{u1}, and covariance σ_{u01}. The ε_{ij} are residual errors, assumed to be independent and normally distributed, conditional on μ_{0-1j} and x, with mean zero and constant variance $\sigma^2_{\varepsilon 0}$. The u_{0j} and u_{1j} are assumed to be independent of ε_{ij}.



out). To be certain, a function of the variance-covariance estimates can be used to plot the between-individual variance against age. For a linear trajectory model, the function follows a quadratic form:

$$\mathrm{var}\left(\mu_{0j} + \mu_{1j}x\right) = \sigma^2_{\mu 0} + 2\sigma_{\mu 01}x + \sigma^2_{\mu 1}x$$

Because the level 2 variance changes over age, the proportion of the total variance that occurs at level 2, called the variance partitioning coefficient (VPC),[23,24] also changes over age:

$$\mathrm{VPC} = \frac{\text{level 2 variance}}{\text{total variance}} = \frac{\sigma^2_{\mu 0} + 2\sigma_{\mu 01}x + \sigma^2_{\mu 1}x}{\sigma^2_{\mu 0} + 2\sigma_{\mu 01}x + \sigma^2_{\mu 1}x + \sigma^2_e}$$

With child growth data, the proportion of total variance that is due to between-individual differences should consistently be high because the within-individual variance is essentially error and should be small. A proportion lower than 80%–90% would indicate that there is a large amount of measurement error in the data or, more likely, that the model needs to be further developed to fit better individual growth curves.

Selecting children who have a certain number of measurements spanning a certain age range may be prudent in some scenarios, but it is not a requirement for multilevel modeling. The serial anthropometric data do not have to be balanced. Children can have a different number of observations occurring at different ages, under a missing at random assumption (i.e., the probability of an observation being missing is related to other observed variables).[25,26] Statistical programs efficiently handle non-consistently collected data using probability functions to describe the relative likelihood of each random effect occurring at a given point in the observation space. The best linear unbiased predictions of the level 2 residuals are shrunk toward the mean, with estimates for individuals with fewer observations having greater shrinkage.[27,28] This means that growth curves for children with less data are constrained to be more like the average curve. Multilevel models, implemented in a frequentist framework, can thus be seen as a precursor to Bayesian approaches, which allow more control over how prior information is used to shrink residuals.[29]

For most physical measurements and periods in the life course, a linear trajectory model will not suffice. It was only used here as an introductory example and the reader should be aware that the in-text equations (e.g., for the VPC) become more complicated with more complex age functions and non-linear models. While it might be ideal to allow every term in a selected age function to have a random effect, and for each covariance to be freely estimated, convergence might not be achieved with such a "maximal random effects model".[30] In this scenario the scientist must normally choose between removing random effect(s), constraining covariance(s) to be zero, or reverting to a simpler model.

Between-individual differences

Level 2 variables vary between-individuals but are constant across age (e.g., sex and ethnicity), whereas level 1 variables can differ from observation to observation within an individual (e.g., date of measurement and nutritional intake). Both can be added into the fixed effects part of a multilevel growth curve model in exactly the same way that independent variables are entered into a conventional regression model. One consideration specific to multilevel modeling is whether level 1 variables should be "grand-mean" centered (i.e., observation$_{ij}$ − sample mean) or "group-mean" centered (i.e., observation$_{ij}$ − individual mean$_j$). The latter approach is not common in multilevel growth curve modeling, but the interested reader is directed to the publications of Kreft et al.[31,32]

The primary reason for incorporating additional variables, other than the age function, into a model is to investigate systematic differences between-individuals in growth. Including sex, for example, and its interaction with age would quantify how the intercept β_0 and slope β_1 are different for girls compared to boys (or vice versa). In this instance, the average growth curves for boys and girls would approximate those obtained by modeling the data for each sex separately. One of the less well considered consequences of doing this for continuous variables is that linear constraints are imposed which may not be realistic. Nonetheless, by incorporating interactions between a variable and all the age terms in a model, you are essentially allowing the average curve to be different at any given value of the variable. Of course, with a level 1 variable, the average curve will be different and can be plotted according to any given value of the variable at any given point on the age scale (e.g., for date of measurement, the curve could be plotted where age 0 years occurred on 20th March or where age 1.5 years occurred on 23rd September).[33] With level 1 variables, the researcher also has to decide whether they should have random effects and, if so, whether covariances (with the other random effects for the growth function) should be freely estimated or fixed to zero. Most statistical packages allow the user to have this level of control over the structure of the level 2 variance-covariance matrix.

The secondary reason for incorporating key explanatory variables into a multilevel growth curve model is that it tends to improve the fit of the individual curves and reduce model error and thus level 1 variance. It is therefore normally a useful exercise even if the research question is not about systematic differences in child growth per se.

Within-individual differences

A standard assumption of multilevel growth curve modeling is that the level 1 residuals are uncorrelated. This assumption will be violated if you don't find the right curve for the process (e.g., if you try to model the adolescent growth spurt using a quadratic

polynomial). In this scenario, a better age function needs to be selected. But even if a good age function is used, the assumption of uncorrelated level 1 residuals may not be reasonable when measurements are taken close to together in time. The resulting serial correlation (i.e., a positive residual tending to be followed by another positive residual etc) can be explicitly modeled in a number of ways. Perhaps the most common and intuitive approach is to extend the model to include a first-order autoregressive (AR1) error structure:

$$\mathrm{cov}\left(e_{ij}, e_{i'j}\right) = \rho^{|i-i'|}\sigma_e^2 \quad \text{if } i \neq i'$$

Here, the covariance between level 1 residuals at any two discrete times i and i' (e.g., visit 1 and visit 5) is controlled by an estimated correlation coefficient (ρ). By raising the correlation coefficient by a power, determined by the difference between i and i' (e.g., $5 - 1 = \rho^4$), the autocorrelation decreases as the gap between i and i' increases. The restriction of this approach is that imposing discrete equally spaced time points may lead to inefficiency and biased estimates. Those interested in more complex autocorrelation functions that allow age to be treated as continuous are directed to a landmark paper by Goldstein et al.[34]

Another assumption regarding the within-individual differences is that the variance between observations within a child is constant. This may not be a reasonable assumption if, for example, some data were self-reported rather than measured, or different equipment was used for different observations, or measurement protocol changed (e.g., supine length before age two years and standing height thereafter). In all of these scenarios, it would be reasonable to expect the level 1 residuals for a child to demonstrate systematic differences. In a multilevel framework, these systematic differences can be explicitly modeled by allowing the level 1 variance to depend on explanatory variables (known as complex level 1 variation).[35,36] The simplest example is to imagine that the level 1 variance is modeled as a function of a binary variable (e.g., self-reported = 0, measured = 1), which is equivalent to having an error term for each response:

$$\begin{bmatrix} \varepsilon_{0ij} \\ \varepsilon_{1ij} \end{bmatrix} \sim N(0,\ \Omega_\varepsilon): \quad \Omega_\varepsilon = \begin{bmatrix} \sigma^2_{\varepsilon 0} & \\ 0 & \sigma^2_{\varepsilon 1} \end{bmatrix}$$

The resulting level 1 variance-covariance matrix looks very similar to that for level 2, with the exception that in this example the covariance is zero because no single observation was both measured and self-reported. It is easy to see how this matrix could be extended for any level 1 or level 2 variable with discrete responses. It is also, however, possible to allow the within-individual variance to vary according to continuous variables, in exactly the same way that between-individual variance can vary according to continuous variables (e.g., age).

A final noteworthy extension to the standard assumptions of uncorrelated level 1 residuals and constant level 1 variance, is to explicitly model how the within-individual variance differs between children. The method proposed by Hedeker et al. includes modeling the logarithm of the level 1 variance as a linear function of explanatory variables (i.e., complex level 1 variation), with an additional random effect that describes how the level 1 variance itself differs between children.[37] The additional random effect is included in the level 2 variance-covariance matrix, thereby allowing investigation of how it is correlated with the conventional random effects describing between-individual variation in growth. This is known as the "mixed-effects location scale model" and can be (and has been) implemented in both frequentist and Bayesian frameworks.[38–40]

Distal outcomes

In addition to modeling the within-individual and between-individual variation in child growth, researchers are often interested in the how different growth traits are related to future or distal outcomes (e.g., adulthood blood systolic pressure). If the random effects are easily interpretable (e.g., μ_{0j} might represent weight at age 5 years and μ_{1j} might represent the yearly rate of weight gain between ages 5−10 years), then they can be used in secondary analyses. The problem with this so-called "two-stage approach" is that uncertainty in the random effects is not taken into account in the confidence intervals for their associations with the distal outcome. Standard errors in the second stage, therefore, tend to be underestimated and type 1 error inflated. One solution is to conduct the entire analysis in one-stage, by simultaneously estimating (1) the multilevel growth curve model and (2) a single level random intercept model for the distal outcome.[41] The level 2 variance-covariance matrix would now additionally include a variance term for the distal outcome and, importantly, covariances with the terms capturing individual variation in growth. This matrix can be manipulated to obtain estimates of the associations between the random effects (e.g., how a one unit increase in weight at age 5 years is associated with adulthood systolic blood pressure) and standard errors can be obtained, albeit with assumptions.[42] Building on this idea, more complex methods are available for simultaneous multilevel modeling of two or more longitudinal processes (e.g., weight and height)[43,44] and joint modeling of longitudinal and time to event data.[45,46] Finally, joint modeling to relate the level 1 variance to a distal outcome is also possible.[47]

If the growth trait of interest is not directly estimated as a model parameter (e.g., adiposity rebound), it can usually be computed using the fixed and random effects that govern everyone's curves. Some studies have weighted the second stage of analysis by the number of serial observations used in the initial growth curve fitting process,[48] but the extent to which this corrects for the problem of uncertainty in the derived trait is not currently known.

Growth mixture models

One key assumption of multilevel growth curve models is that all individuals are drawn from a single population and that a single average growth curve adequately approximates the entire population. Given our knowledge of human growth, this assumption may often be unrealistic. During infancy, for example, we know that about 40%–60% of infants demonstrate canalization or centile tracking from birth, while the rest are split between those with upward centile crossing and those with downward centile crossing.[49,50] These groups or sub-samples should arguably have their own average curve, with individual deviations around them. Such a model would not only provide a better fit to the data (compared to a model with a single average curve) but would also serve to group people together who share the same average trajectory. While we might hypothesize that there are three sub-samples, there might be less or there might be more. And while some individuals may very clearly belong to one sub-sample, others might not. Growth mixture models are a very flexible, but equally challenging method used in auxological and obesity epidemiology to identity unobserved or latent classes of individuals who share similar growth curves.[51,52]

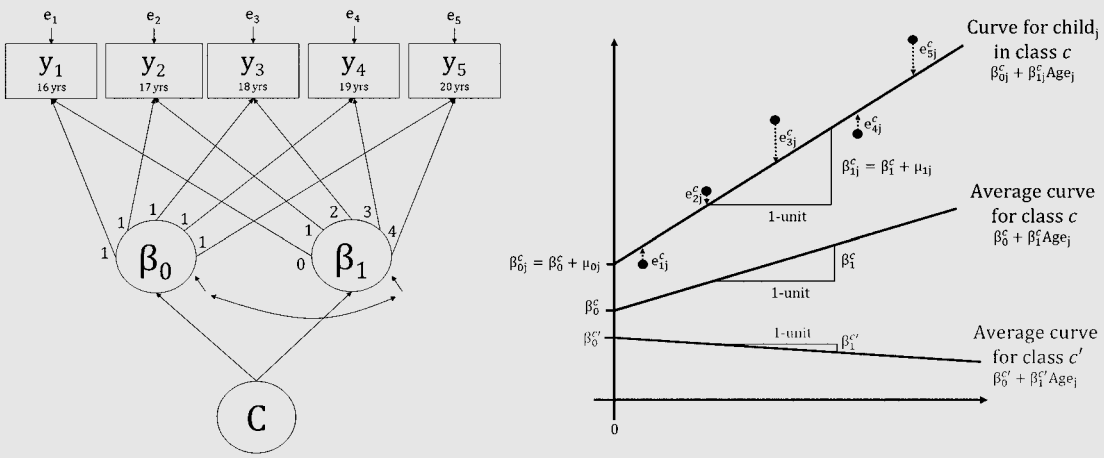
Key principles

Growth mixture models relax the assumption that all individuals share a single average trajectory by combining a latent growth curve model with a categorical latent variable.[53,54] Latent growth curve models are a special type of structural equation model (SEM), where the parameters that govern the shape of the curve of each child in a sample are estimated as latent or unobserved variables using confirmatory factor analysis. In most instances, a latent growth curve model can be fitted as a multilevel growth curve model (and vice versa), producing analytically and empirically identical results.[55,56] For this reason, they are not covered in this book chapter. Readers wanting to know more about latent growth curve models are directed to Bollen & Curran's textbook.[57] In particular, chapter four provides a detailed review of how to code the factor loadings to produce non-linear trajectories (e.g., polynomials and piecewise linear splines).

In the SEM framework, the age scale is treated as being a series of discrete time points, with no individual variation in the ages of measurement. Techniques are available to handle irregular measurement ages, but the increases in computational time can be colossal. Ideally, therefore, all children in a sample will have measurements at the same or essentially the same ages. Converting the outcome to Z-scores, in an attempt to account for age differences, is not recommended as this will, at least theoretically, affect the latent classes.

The illustration in the left-hand side of Box 13.3 is a schematic of a linear trajectory growth mixture model, where the outcome was measured yearly between 16 and 20 years

Box 13.3 A linear trajectory growth mixture model



of age. The factor loadings for the slope β_1 represent the underlying time scale. The intercept β_0 applies equally across the time points, and thus the factor loadings are all 1. As with a multilevel model, there is error (e_{1-5}) and covariance between the latent growth curve terms β_0 and β_1, as indicated by the curved line. What makes this a growth mixture model, however, is the regressions of the growth terms on a set of dummy variables representing the categories of the latent class variable C (i.e., the number of latent classes in the population). This number is specified by the scientist and is distributed with the probabilities:

$$p_c, \;\; c = 1, \;\; \ldots, \;\; C, \;\; \text{with } 0 \leq p_c \leq 1 \;\; \text{and} \;\; \sum_{c=1}^{C} p_c = 1$$

Put simply, each class has a probability of between 0 and 1, that sum together to equal 1. The model is a generalization of a linear trajectory multilevel model, and has an equation that follows the same basic form:

$$y_{ij|c} = \beta_{oj}^{c} + \beta_{ij}^{c} x_{ij} + e_{ij}^{c}, \quad \text{for } \; c = 1, \ldots, C$$

The parameters are defined as in Box 13.2; the difference being that here they are different for each class. This means that the observed data are described using a multilevel model that is specific to each latent class, with the joint distribution of the data then being a

mixture of these distributions, weighted by the probability of each class, p_c.[51] Extensions are available for non-normal data, such as BMI, and categorical outcomes, such as Tanner stages of pubertal development.[51,58]

The illustration in the right-hand side of Box 13.3 demonstrates how the parameters describe the trajectory for a theoretical child with five serial measurements, who belongs to class c. The average trajectory for a second class, c', is also shown. Each individual has a posterior probability of belonging to each latent class but can be assigned to a single class that they are most likely to belong to (i.e., "modal assignment"). The child represented in Box 13.3 would clearly have a higher probability of being in class c than c', and would be assigned as such. Ideally everyone would have a very high probability for one class and very low probabilities for the other classes. This degree of separation between class membership is summarized by the entropy statistic.[59] Entropy values vary between 0 and 1, with greater values indicating clearer separation between latent classes.

Estimation and replication

Because the classes are unobserved, estimation of growth mixture models is performed by maximum likelihood, with the expectation−maximization algorithm.[60] This iterative estimation process seeks to minimize the negative log-likelihood. With such complex models, however, risk of converging to local minima is high and increases as the number of classes increases.[61] Estimation is therefore performed using multiple random starting points. Those that converge at the lowest, same negative log-likelihood have replicated and are likely to have found the global minima. This estimation process means that growth mixture models are computationally intensive and can take a long time (think days not hours) to run. This is particularly true if the model is fully developed.

Default and user-specified constraints

Given the difficulty of estimation, most statistical programs constrain certain aspects of a growth mixture model by default. In Mplus, for example, the estimates for the variance-covariance matrix for the growth terms are constrained to the same in each class.[62] While a separate error or residual variance term is estimated for each time point (i.e., non-constant error of heteroskedasticity is assumed), they are also constrained to be the same in each class. In some instances, these constrains may be realistic and for other they might be unrealistic. For BMI, for example, one would probably expect classes with higher trajectories to have greater variance, both in terms of the intercept and the errors. This could be achieved by removing some of the default constraints, although doing so often results in estimation problems. Indeed, for a growth mixture model with a non-linear trajectory to converge, the researcher normally often must start by adding constraints

rather than removing them. It is, for example, common practice to constrain some of the growth terms (e.g., the cubic term in a cubic polynomial) to have zero variance and thus no covariance with the other growth terms.[63] Another approach is to constrain the less important covariance terms (e.g., between the quadratic and cubic term) to be zero.[64] If all of the growth terms are constrained to have zero variance (and thus no covariance exists) then the model is a latent class growth model, also known as a group-based trajectory model.[65] This can be thought of as a special case of the growth mixture model. Some user-written commands implement latent class growth models rather than growth mixture models per se.[66] The problem with the former is that the assumption they make (i.e., no individuals differences in growth within a class) is entirely unrealistic. By constraining growth terms to have zero variance, not only does the model fit worsen, but the researcher also introduces autocorrelation among the residuals, which should be (but very rarely is) explicitly modeled.[63,67] Further, the average trajectories and composition of classes (e.g., model assignment: 75% in class 1 and 25% in class 2) in a latent class growth model, or heavily constrained growth mixture model, can be very different from those from a carefully developed growth mixture model.[68]

Model development, selection, and reporting

Different papers have been published on the steps that should be taken in the development of a growth mixture model,[69] although the order and importance of each is up for debate. My general advice would be to fit a set of, say, 1−7 class growth mixture models in the following steps. Firstly, compare different appropriate age functions with default constraints and adding additional constraints if necessary, starting with the least imposing. Secondly, using the selected age function, try to relax the constrains in order what of you believe to be most unrealistic. Thirdly, if you have had to constrain the variance-covariance structure, consider the need to model the resulting random error structure.[63] Alternatively, some experts argue it might be better to start with a model that properly accounts for the data generating mechanism (e.g., weight at time 1 will cause weight at time 2 etc.) underlying the random structure.[70] Regardless, the choice of which model to take forward through the steps in any model development should be guided by an appropriate measure of model fit, such as the Bayesian Information Criterion (BIC), not entropy.

Once the structure of the final model has been developed and the different solutions have been fitted, the researcher is faced with the challenge of selecting the most likely number of classes. This is normally based on a combination of factors including overall fit according to metrics like the BIC, the quality of classification or separation between the classes, and the plausibility and interpretability of the average trajectories. Bootstrapped likelihood ratio tests (BLRTs) can be used to obtain p-values comparing each *C* class

model with the $C - 1$ model,[71] but selection of a model based solely on $p < 0.05$ (or some other threshold) is obviously very poor practice. For solutions with $C > 1$, ideally each class would have an average trajectory and composition (e.g., 75% of the sample) that matched with theory, have a high mean posterior class membership probability (>0.65 is one proposed cut-off), and contain a meaningful number of individuals (>5% of the sample is one proposed cut-off).[72]

In terms of what to present, the Guidelines for Reporting on Latent Trajectory Studies (GRoLTSs) reporting checklist is an excellent tool.[73] Following it will ensure not only that the right information is presented, but also that the modeling has been thorough and considered the relevant points above.

Epidemiological investigation

The ways in which growth mixture models can be extended (e.g., to consider two parallel growth processes) are too numerous to cover in this book chapter. Adding regressions of the growth terms on explanatory variables (e.g., sex or ethnicity) is possible and these estimates can be allowed to vary across each latent class. Another common consideration in epidemiology is how best to investigate the determinants and distal outcomes of class membership. While it is possible to do this by adding auxiliary observed variables directly into the growth mixture model, this "one-step" approach is problematic because specifying relationships between the latent class variable and auxiliary observed variables can affect the formation and meaning of the latent class variable.[74] Instead, and particularly for distal outcomes, it is common practice to extract the modal assignment for each individual and use that variable in separate, secondary analyses. This is known as a "three-step" approach as it involves estimating the growth mixture model, extracting the modal assignments, and then using them in separate, secondary analyses. One way that is commonly used to account for the uncertainty in the modal assignments is to weight the separate, secondary analysis models by the posterior probabilities of most likely class membership. However, more sophisticated three-step approaches have been developed, such as the BCH method (named after Bolck, Croon, & Hagenaars),[75] and these are likely to become increasingly popular as fully automated procedures are developed and incorporated into software.

Concluding remarks

This book chapter has focused on two methods widely used to study child growth curves, namely multilevel and growth mixture modeling. The references should serve as a starting point for further reading and learning. One method that has not been mentioned is functional data analysis,[76] which might be particularly useful for very frequently collected data.[77] Although this method can be (and has been) applied to the type of data that are

typically collected in growth studies,[78] it was not covered in this chapter because it is a far less common approach than multilevel growth curve modeling. The reader should also be cognisant that, in some instances, it may not be prudent or necessary to fit growth curves. A broader overview of strategies for handling growth data can be found in my 2015 paper in the American Journal of Human Biology.[79]

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CHAPTER 14

Growth references and standards

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Introduction

Purpose

To measure the height of an individual we use a calibrated instrument called a ruler. We assess the height status of an individual in just the same way, with a form of calibrated instrument called a growth reference. But there is an important difference between measuring a child's height and assessing their growth status. Rulers generally agree about how long a meter is, but an individual's growth rate depends on a wide variety of factors including their sex, age, pubertal stage, parental size, ethnicity, health, socio-economic status and so on. The ruler to assess it needs to be multidimensional to handle all the relevant factors. This is the role of the growth reference, to provide a way of displaying expected growth as a function of (some of) these other factors in a compact, accessible and visually appealing form.

Growth and size

It is important to be clear about the distinction between growth on the one hand and size on the other. Growth is strictly speaking a form of *velocity*, the rate of change in size over time, and it requires measurements on at least two occasions to assess it. Size conversely is based on a single measurement. The term "growth chart" is unfortunate in that most growth charts do not assess growth at all, they measure size. Tanner proposed that, by analogy with growth and velocity, charts measuring size should be called "distance" charts — they measure the *distance* the child has traveled on the journey from conception to adulthood. As we shall see later, most distance charts not only fail to assess growth, their underlying reference data even lack any information about growth. Nevertheless, to avoid confusion, this chapter follows common practice by referring to size or distance charts as growth charts.

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Chart form

A growth reference is essentially a database defining the statistical frequency distribution of one or more measures of size and/or growth, indexed by age and sex, based on a reference sample of children. The information may be summarized in a table, but for clinical purposes it is usually presented as a chart plotted against age. This form of presentation has developed over the last hundred years or so.[1,2] An important principle of growth charts is that the curves making up the chart – the chart *centiles* – should appear smooth.

The word *centile* is a shortened form of *per-centile,* a concept invented by Francis Galton back in 1885.[3] The word subsequently simplified to *percentile* and is widely used for growth charts, particularly in the USA, while the alternative *centile* is preferred elsewhere in the world. Of the two, c*entile* is both simpler and more consistent with the other quantiles that are in current use, e.g. tertile, quartile, quintile and decile. The only other "per-" quantile besides percentile is the obscure *permillile*. For these reasons the term *centile* is used here.

There are 99 centiles, the points on the frequency distribution that split it into 100 equal parts. Centiles are numbered upwards from 1 to 99 and indicate whereabouts in the distribution a child's measurement is to be found, given their age and sex. The 50th centile, also known as the median, is the mid-point of the distribution, with 50% to the left of it and 50% to the right. The third centile has 3% to the left of it and 97% to the right. In the simplest case, where the frequency distribution is normal or Gaussian, the centiles are in one-to-one correspondence with the distribution's mean and standard deviation (SD). So the centiles can be calculated from the mean and SD.

A centile *curve* is a curve joining up the values of a specified centile at different ages. So the percentage chance of a reference child's value lying below a specified centile curve is given by the centile's label, e.g. 3% chance below the third centile curve. In addition this chance is the same at all ages, so long as the child comes from the reference population on which the chart is based.

Centile curves are drawn on the chart to represent the distribution at each age. When selecting which centiles to include, one approach is to base them on the underlying SD. This is the pattern used for the WHO 2006 growth standard from 0 to 5 years of age,[4] seven centile curves corresponding to the mean, 1 SD above and below the mean, then 2 SDs and 3 SDs similarly. So the curves are symmetric about the mean and spaced 1 SD apart. The centiles they correspond to are (when rounded) the 0.1st, 2nd, 16th, 50th, 84th, 98th and 99.9th. With a normal distribution the 50th centile or median coincides with the mean. Note that the two extreme centiles need an extra decimal place of precision, as the distribution is stretched in the tails and the regions beyond the 1st and 99th centiles extend to ± infinity.

The British 1990 reference [5] and its successor the UK-WHO growth charts for age 0–4 years,[6] based on the WHO standard,[4] uses a format based on nine centile curves that are spaced two-thirds of an SD apart. This spacing corresponds to the 0.4th, 2nd, 9th, 25th, 50th, 75th, 91st, 98th and 99.6th centiles.[7] Note again that the centile labels are rounded not exact. With a normal distribution such as height these SD-based curves appear equally spaced on the chart at each age.

When the distribution is not normal, so that the mean and SD are insufficient by themselves to define it, the frequency distribution can be specified in terms of empirical centiles, estimated directly from the data. But this is less efficient, as the mean and SD are estimated more precisely than individual centiles.[8]

A widely used set of empirical centiles is the 3rd, 10th, 25th, 50th, 75th, 90th and 97th, which are close to the middle seven centiles of the nine-centile format described above. The 5th and 95th centiles are also used. The advantage of the nine-centile format over these empirical centiles is that the 0.4th and 99.6th centiles provide extra resolution in the tails of the distribution, which is where most growth morbidity is to be found. Cole[7] discusses reasons why particular centile sets are used.

Assessment

The curves on the chart represent either centiles or fractions of an SD above or below the mean. The assessment of individual subjects follows the same principle. The subject's measurement is plotted on the chart and the corresponding centile or SD relative to the mean is read off it. Take a girl aged 3 years who is 90 cm tall – her height is on the ninth centile of the UK-WHO reference, just above the ninth centile on the chart, and it corresponds to 1.33 SDs below the mean. By convention the child's SD position on the chart is known as the SD score, or SDS, or z-score.

There has been much debate about the pros and cons of using centiles versus SD scores for assessing growth. Centiles are on a scale from 1 to 99, centered on 50 (0 and 100 are off-scale), whereas the SD score scale is centered on 0 with an SD of 1. Centiles are easier for subjects and their parents to understand, whereas SD scores are preferred by research professionals as they are better behaved statistically. In addition they provide greater resolution than centiles in the tails of the distribution. The WHO growth standard for example, with its centiles 1 SD apart, is better-fitted to quantify the size of malnourished individuals whose weight lies well below the third centile. The 3rd, 1st and 0.1st centiles for example correspond to SD scores of −1.9, −2.3 and −3.1 respectively, so that the region between the −2 and −3 SD curves on the chart corresponds to a very narrow centile range. Equally in the upper tail of the distribution, it is not uncommon for obese individuals to have a body mass index (weight/height^2 in kg/m^2) exceeding the 99.9th centile, so SD scores are necessary to provide extra resolution.

A third scale of assessment is "percent of the median", where the measurement is expressed as a percentage of the median value for the child's age and sex. This is used mainly in the developing world to assess nutritional status, and is a simpler version of the SD score. An SD score of 0 always corresponds to 100% of the median, but an SD score of −2 corresponds to different percentages of the median depending on the measurement − e.g. 92% of the median for height but only 80% for weight. The percent of the median, unlike the SD score, does not take into account the variability of the measurement.

So a child's position on the chart can be expressed as a centile, an SD score or a percentage of the median. The secondary purpose of the chart is to follow the child over time and see how their growth status changes. Often, they stay close to their previous position but in general they change position, possibly quite dramatically, i.e. they *cross centiles* up or down. The chart is particularly useful for visualizing centile crossing. It would also be useful if the chart indicated when the degree of centile crossing was excessive, but unfortunately it lacks this information. To assess centile crossing a velocity chart is needed, as is discussed later.

Unconditional and conditional references

Some growth references are called "conditional," meaning that the reference data are *conditional* on, or adjusted for, some specified factor. Examples are references conditional on growth tempo or mid-parent height. But it is a misleading term as all growth references are conditional to some extent − they adjust for age and sex if nothing else. "Conditional" is taken here to mean conditional on factors over and above age and sex. References for velocity are a particular and important case of conditional references.

Structure of chapter

The process of developing growth references involves four main stages: first the choice of the reference population; then the drawing of the sample; then data collection, cleaning and analysis, and finally the design and production of the chart. The chapter follows the same sequence. Conditional references, which involve different statistical principles from unconditional references, are discussed separately.

Defining the reference population

The choice of reference population is one of the most important decisions to make when developing a growth reference. It relates to how the reference will be used, by whom and on which subjects. There are two key questions: Is the reference to be used primarily as a clinical or as a public health tool? And is it intended to reflect "optimal" or "typical" growth?

Clinical or public health tool

For doctors, nurses or health visitors involved in the care of individual children the growth chart is an essential part of their clinical toolkit. The child's measurement centiles are a direct measure of health, and the medical assessment of the child involves interpreting the centiles. If the child is not representative of the chart's reference population, the centiles will be biased and the growth assessment may be invalid.

For public health purposes the applicability of the chart to the individual child is less important. The aim is to summarize the nutritional status of a *group* of children, with a view to comparing the group with other groups (e.g. by socioeconomic status), so that the position of the individual child, or indeed the group, on the chart is not the primary concern.

These alternative aims are contradictory. The first requires the chart to be appropriate for the child, while the second applies to different groups of children, and it cannot be appropriate for them all. This fundamental contradiction lies behind many arguments about the use of growth charts. In practice there is a compromise where the chart can be useful both clinically and in public health terms – see below.

For clinical use the chart's reference population needs to be clearly defined in geographical, cultural and/or social terms. An example is the British 1990 reference,[5] which was representative of ethnic white children living in England, Scotland and Wales in 1990. "White" was originally specified because ethnic groups differ in their growth pattern. An obvious disadvantage of this definition is that British ethnic minority children are excluded from the reference, which implies that they need ethnic-specific references of their own. But in practice there are many different ethnic minorities, and the alternatives are compounded by ethnic mixing, so that separate charts for all are impractical. The compromise is to use the British chart for everybody, irrespective of their ethnic makeup, but to introduce ethnic-specific adjustments where necessary to extend the coverage to ethnic minorities.[9] These adjustments can be estimated on relatively small samples of children, and far fewer than needed to derive a full growth chart.

Other examples of charts for clinical use are syndrome-specific charts, e.g. for children with Down syndrome[10] or Turner syndrome.[11] Their growth is known to differ from that of children without the disorder so the syndrome-specific chart is appropriate. Another example is a chart for breast-fed infants, who grow differently from formula-fed infants. But this is a less clear-cut example, as the mother's decision whether or not to breast-feed is not only a social but also a health issue. And this relates to the question of references versus standards – see the next section.

For public health use the chart does not need to be based on any particular group, so long as it politically acceptable. Charts representative of the national population are widely used, like the British 1990 chart, but in principle a single chart for the whole world could be just as useful. Unfortunately politics tends to intrude at this point, and developed countries have in the past preferred to use their own charts rather than work toward international comparability. However the advent of the WHO 2006 growth standard changed attitudes in this respect, and many countries (including several developed countries) have now either endorsed or actively adopted the WHO standard for national growth assessment in the early years of life.[12]

Reference or standard

In addition to selection by geography or ethnic background, the reference population can also be identified on health grounds, excluding children for example with a growth disorder. The assumption here is that the growth portrayed by the chart is better than for the unselected population, and so is in some sense optimal. In this case the growth reference is known as a growth *standard* rather than a reference. (Growth references based on unselected populations used to be called standards, and they occasionally still are, but strictly this usage is incorrect.)

References based on healthy subgroups, i.e. standards, can be contentious. Take three examples, of birthweight in premature babies, height in children with Down syndrome and growth in elite groups in the developing world.

Among babies who are born preterm, those who are induced tend to be sicker and hence lighter than babies delivering spontaneously at the same gestational age. For this reason some argue that birthweight standards should exclude preterm babies who have been induced. But this ignores the fact that all preterm babies are to some extent unhealthy – they are born earlier than expected. Cole et al.[13] discuss this in more detail.

Similarly with Down syndrome, where up to a third of children are born with cardiac defects that can materially affect their growth. Most defects are now corrected within the first year, but some children remain appreciably growth retarded later in childhood. Again the case is made to exclude from the reference those with serious cardiac defects.

Children in the developing world of high socio-economic or "elite" status are known to grow better than their poorer contemporaries. Indeed they can grow as well as children in the developed world.[14] This has been the motivation for some developing countries, e.g. India, to base their national growth standards on elite children.

Although there are advantages in restricting the reference population on health grounds, there are also disadvantages. Firstly, if the chart is restricted to a healthy subset of children, how, logically, does one assess the growth of those children that have been excluded? By definition the chart is not appropriate for them, as it portrays growth in children who have been selected to grow better on average.

Against this, elite standards, it is argued, show how the child *might* grow if their socio-economic status were to be raised. The chart documents the *potential* for growth. This is the basis of the WHO 2006 growth standard, which aims to define normal growth in terms of breast-fed children with unconstrained growth. But this same argument cannot be applied to induced preterm babies or Down syndrome children with cardiac defects – in each case their status is immutable and the chart will never be appropriate for them.

The second disadvantage of growth standards is the need to define *health*. Criteria are required to identify which reference subjects to include and which to exclude on health grounds, and this is inevitably arbitrary. The examples above happen to have fairly clear-cut criteria (though the severity of cardiac defect in Down syndrome children needs to be quantified), but often this is not the case. For example should one exclude children with asthma, or renal disease, from the reference population? These conditions affect growth in some children but not others. The case can be made either way, to include or exclude them, but ultimately it is arbitrary.

In the developed world, growth assessment tends to be simpler using a reference than a standard, so that all children are eligible for the reference dataset irrespective of their health status. Against that, the advent of the WHO growth standard for age 0–5 has strengthened the case for using a standard, and several countries including the UK have included the WHO standard as part of their national charts. Its strengths are that (i) it represents the growth of breast-fed infants, whereas a reference necessarily documents the growth of a mix of breast- and formula-fed infants, which leads to bias when breast-fed growth is the norm; and (ii) it defines a relatively low "plane of nutrition" in the first two years, as the WHO reference children were relatively light and thin. Thus it tends to highlight children who are overweight rather than underweight when applied to other populations, and at a time when child obesity is an increasing concern, this represents an appropriate shift in emphasis.

Drawing the sample

Having settled on the reference population, the next stage is to decide on the study design. This involves answering such questions as these: is the focus of the study growth distance or growth velocity? How big should the sample be? How should the sample be chosen?

Design: cross-sectional, longitudinal, mixed-longitudinal?

The most common form of growth study is the cross-sectional survey. This collects data on children over a range of ages, each child contributing a measurement on a single occasion. Such a design is conventionally called a growth survey, but it contains no information about growth velocity as each child is seen only once.

To assess growth velocity the survey needs to measure subjects at least twice. Where all subjects are measured repeatedly this is a longitudinal design, while if only some subjects are remeasured this is a mixed longitudinal design. Longitudinal designs are more costly than cross-sectional designs for several reasons: they last for a longer time, they have to maintain contact with the subjects, and often it is cheaper to keep highly trained staff employed than to recruit new staff at each measurement occasion.

Longitudinal designs provide information on not only mean growth velocity, but also its variability. Cross-sectional designs can estimate the mean annual growth rate through the difference in size of successive year groups, but this provides no information about the variability of growth velocity in individuals. In addition it gives a biased assessment of growth velocity during puberty, where cross-sectional data flatten the peak in the velocity curve.[15]

The main difference between a longitudinal and a mixed longitudinal design is the time period over which velocity is assessed – longitudinal designs cover longer periods. If velocity over one year is the main concern, then two successive cross-sectional surveys one year apart, with say 50% of subjects measured on both occasions, is a mixed longitudinal design that provides all the required growth velocity information. Tanner[16] discussed this design in some detail and highlighted its statistical efficiency.

Longitudinal designs, with infants recruited at or before birth and followed up for extended periods, have been popular in the past but are less so now. See for example the coordinated studies carried out during the 1950's in London, France, Switzerland and elsewhere.[17] Their main advantage is that they provide complete growth curves for individual children, which cannot be obtained in any other way. But longitudinal designs are expensive, for the reasons described above, and mixed designs have now tended to take their place.

The age range of the data is another important aspect of the design. Should it start at birth? If so should it include some premature births? Should it extend to adulthood? When *is* adulthood – 18, 20, 25 years? The answers to these questions may relate to the ease or difficulty of obtaining the sample at particular ages. These issues need to be addressed at the outset.

Sample size

The estimation of sample size through a power calculation is standard practice in medical research, yet it is surprisingly difficult to apply to growth studies. Traditional sizes of growth study have developed over the years, but they are difficult to justify statistically. A common rule of thumb is a sample containing 200 to 300 subjects per age group. This is broadly speaking the size of the European longitudinal growth studies of the 1950's and 1960's, with larger numbers recruited and rather smaller final sample sizes. Yet statistically the number is hard to justify. In addition it is not helpful in a cross-sectional study when the width of the "age group" can be anything from one month to one year.

The WHO Multicentre Growth Reference Study[18] used the criterion of 200 subjects per 3-month age-sex group for a longitudinal design from birth to 2 years (i.e. 200 subjects per sex altogether), and a similar cross-sectional design over the age range 18 months to 6 years, giving a sample size of 800 per year. Extrapolated to 0−20 years this implies a sample of 16,000 subjects per sex, which is substantial. In practice many surveys are appreciably smaller, even down to one-tenth the size. Empirical evidence from fitting growth centiles to surveys of different sizes suggests that a survey of say 2000, or 50 per year per sex from 0 to 20 years, estimates the mean and median with high precision, but the outer centiles with only moderate precision.

A recent study has formally explored sample size calculations for growth reference studies.[19] It arrives at three main conclusions: that a) the sample size needed is smaller than might be expected due to the smoothing applied to the centiles; b) the precision specified to define the sample size should be measured on the SD score scale not the measurement scale, and c) the sample composition, i.e. the age distribution of measurements, needs to be optimized simultaneously with the sample size. In terms of precision, for a sample size of 7000 from birth to 20 years the standard error of the median is around 0.04 SD score units, rising to 0.065 units for the 98th centile. These correspond to 95% confidence intervals of 47−53 for the median and 1.7 to 3.1 for the second centile. To achieve this level of precision across the age range requires more measurements to be sampled in infancy than later in childhood. But the degree of infant over-sampling needed depends on the centile used to define the sample size; relatively speaking the median needs many more infant measurements than the 98th centile. The study concludes that samples of between 7000 and 25,000 measurements per sex provide adequate power.

Weighting by age, or extending the age range

The precision with which the centile curve is estimated varies with age − it is highest in the middle of the age range and lowest at the extremes due to the presence of "edge effects". To compensate for edge effects two strategies are available: one is to oversample

at the extremes, with say 2−3 times as many subjects in the youngest and oldest age groups compared to other ages, and the other is to extend the age range of the data beyond the upper age of the published chart. This latter approach is not available at birth, but at the upper end the age can be increased by say 1−4 years. This ensures that at the upper age on the chart the curves are estimated with adequate precision.

Another age-related issue is whether measurements should be taken at precise pre-specified ages (e.g. at 3 months or 12 months), or whether they should be distributed uniformly within a given age range (e.g. 6−12 months). In the past the statistical techniques available to fit centiles to growth data required measurements to be grouped around specific ages, but this is no longer necessary. Longitudinal studies are usually designed to have a set of target measurement ages, which is administratively convenient, but for cross-sectional surveys, the usual growth reference study design, subjects can be recruited within specified age ranges. The sample size study cited earlier[19] provides guidance on the numbers needed per age group.

Sampling

The subjects in the reference sample should be selected from the target population in a way that ensures generalisability, ideally by random sampling. The sample may be a simple random sample, or it may be a complex multi-stage design involving clusters or strata. For example a national sample might be based on randomly selected clusters of geographical areas, then random households within areas, then random children within households. The advantages and disadvantages of the different designs involve a trade-off between complexity (i.e. cost) and variability (i.e. imprecision of the estimates).

Children of school age can be ascertained through their schools, which is more efficient than working through households. Conversely, children of pre-school age or those who have left school are harder to sample randomly, and this can pose problems for obtaining representative samples over age ranges extending outside school age.

Collecting the data

Having identified the reference population and sample, the next stage is to measure the subjects. This requires decisions about which measurements to make, how to make them and how to ensure their quality.

Select measurements

The choice of measurements depends on the aim of the study. Weight and height (or length in infancy) are obvious choices as they are the two “whole body” measurements,

they require relatively simple equipment to measure them, and taken together they provide a measure of weight-for-height. Weight-for-height can be viewed as "shape" adjusted for "size," and so it is useful to quantify the two extremes of malnutrition, wasting and obesity. However weight-for-height without an adjustment for age can be misleading in early life,[20] and age-adjusted body mass index is better in this respect.

Skinfold thicknesses are a useful proxy for regional body fat, and the contrast of e.g. triceps and subscapular skinfold gives a measure of fat distribution in limbs relative to the trunk. The main disadvantage of skinfolds is the considerable inter-observer variation, which reduces their generalisability. And they can be particularly difficult to measure in obese subjects.

Body circumferences, e.g. around the arm or waist, are simpler to measure than skinfolds, and provide information over and above the other measurements described so far. Arm circumference (also known as mid-upper arm circumference or MUAC) is a useful alternative to weight-for-height for assessing wasting in malnutrition.[21] In addition, arm circumference and triceps skinfold together provide an estimate of arm muscle area.[22] Waist circumference is increasingly important as a risk factor for obesity and its sequelae in children and adults.[23]

Head circumference acts as a proxy for brain size, and is usually of interest primarily in infancy when head growth is maximal.

Body proportions can be studied by measuring sitting height or cristal height (i.e. leg length from the floor to the iliac crest) and expressing it as a fraction of height. Leg length (either as cristal height or the difference between height and sitting height) is increasingly seen as a proxy for growth in early life, and is important in life course studies.[24] Body widths, e.g. biiliac width or biacromial width, are for more specialized anthropometry studies.

Choose location and personnel

The next questions are: who will take the measurements, and where will these observers be based? Depending on the size of the survey, the observers may be existing anthropometrists, school nurses, practice nurses or research nurses, or alternatively they may be recruited specifically for the survey. There may be one measuring team based centrally, which travels to each region in turn, or alternatively there may be teams based in each region that make use of local staff. The measurements can be made in subjects' houses, or alternatively the subjects can be invited to a central meeting place like a clinic or school. The choices will depend on the ages of the subjects, their geographic spread and the cost and availability of staff. The choice between central and local measuring teams will depend on the number of measurement regions, the number of subjects, the time available for the survey and the likely compliance of subjects and/or their parents.

Equipment and technique

Anthropometry is the primary focus of growth studies, so it is essential for the measurements to be of the highest possible quality. This requires attention to the instruments used, their calibration and maintenance, to the training of observers in terms of technique, precision and accuracy, and in particular to quality control throughout the study. For long-term studies this involves regular training sessions where observers meet together to assess intra- and inter-observer variation by measuring and re-measuring small groups of children.

For details of measurement technique and quality control, Weiner and Lourie,[25] Cameron[26] and Lohman et al.[27] give comprehensive accounts.

One way to improve both precision and accuracy is to take replicate measurements. For example taking two measurements and averaging them is a common approach, though it does not protect against the possibility of an occasional rogue measurement. This can be handled by taking a third measurement when the first two disagree sufficiently, but it involves setting an arbitrary cut-off to define exactly what "disagreement" is. A simpler approach is to routinely take three measurements and record the median value; this increases precision with three replicates while avoiding calculating the mean, and it also increases accuracy by protecting against rogue measurements.[28]

Cleaning the data

There is a temptation, once the data have been collected, to immediately start analyzing them — this is a mistake. An important preliminary stage is to *look* at the data, to search out errors of measurement or coding and fix them. Left untended they can seriously affect the validity of the analysis.

Diagnostic plots: marginal and conditional

The key to data cleaning is the inspection of diagnostic plots, which fall into two categories — marginal and conditional. A marginal plot is a plot of one variable on its own, typically a histogram, showing the distribution of the measurement. This plot highlights the presence of any outliers, and also indicates the broad distributional shape of the variable i.e. whether it is normally distributed (bell shaped), or if there is some skewness (one tail, usually the right, longer than the other) or perhaps kurtosis (heavy tails) or bimodality (with two peaks). With suitable software, such as *plotly* (plotly.com) it is possible to draw the histogram, highlight each outlier, check the corresponding data, and correct or eject as appropriate, all very quickly.

Marginal diagnostic plots are useful for identifying the most obvious outliers, but they fail to pick up many others. For example consider a height of 160 cm incorrectly coded as 60 cm. In a data set covering 0−20 years this corresponds to an adult height appearing as an infant length, so a marginal plot will fail to spot it. However a scatterplot of height versus age will cause it to stand out as an obvious outlier. This is a *conditional* diagnostic plot of height on age.

The conditional plot works well when two variables are reasonably highly correlated (i.e. height and age here). It can be very sensitive, and for measurements like height which have a small coefficient of variation and where the correlation is high, it will spot outliers that are far less extreme than the example above.

Weight versus age works nearly as well, except that weight usually has a positively skewed distribution, with the right tail longer than the left. Spotting outliers here is more difficult, as the individual points in the extreme right tail (i.e. at the top of the scatterplot of weight vs. age) are spread further apart, and so appear to be more extreme, than those to the left. It is tempting to treat all those in the right tail as outliers, but this is generally unwise.

To help in the identification of outliers it is useful to have an objective criterion, particularly for outliers that are not obvious. Working with SD scores rather than the original measurements is useful as the age and sex differences are adjusted out, and weight or height for the entire data set can be plotted as a marginal diagnostic plot without involving age.

What is a reasonable range of values for the SD scores? A useful cut-off is ± 5 − the chance of a genuine point outside this range is vanishingly small (3 in 10 million), so even for large sample sizes of 10,000 to 20,000 such points are highly likely to be wrong. For appreciably smaller sample sizes a tighter cut-off of say ± 4 can be used, corresponding to a chance of 3 in 100,000.

The way to deal with outliers is to go back to the original coding form and look for something obviously wrong. In longitudinal studies it should also be possible to check the consistency of the subject's measurements on previous occasions. Often an error will be found which can be corrected. But there will be occasions when the measurement is apparently correct, and the question then is whether or not to retain it in the data set.

There ought to be few such points, so that they can be described and justified on an individual basis when the analysis is written up. Statistically there is a case for omitting them even though they may be correct, if they challenge the statistical assumptions made by the analysis. If the analysis is not robust to outliers it may be seriously affected − an example is regression analysis where a single outlying point can dramatically alter a multiple regression equation.

Estimating distance centiles

Once the data are clean, work can start on fitting the centiles. The process of fitting distance centiles to data involves a series of choices. Is age to be treated as continuous or grouped, e.g. by whole years? Can the measurement be assumed to be normally distributed at all ages, or is some form of adjustment needed? And how should the centile curves be modeled − what form of equation is to be used? In practice all the questions are easily answered.

Age grouped or continuous

In the past it was customary to first split the data into age groups. Within each group the age trend is small and the distribution can be summarized as the mean and SD. These summary statistics can be adjusted for minor age effects,[29] plotted against mean age for each group, and summarized by smooth curves drawn through them, one curve for the mean and one for the SD. Together the two curves allow any centiles to be drawn assuming that the distribution is normal, using the formula

$$Centile_{100\alpha} = Mean + SD \times z_{\alpha} \tag{14.1}$$

where z_{α} is the normal equivalent deviate for the required distance centile 100α, and *Mean* and *SD* are values read off the curves at a particular age. For the median or 50th centile ($Centile_{50}$) where $\alpha = 0.5$ then $z_{0.5} = 0$, while for the third centile ($Centile_{3}$) $z_{0.03} = -1.88$. Values of a given $Centile_{100\alpha}$ for a series of ages can be plotted against age to give the required centile curve.

However nowadays age is better treated as a continuous variable rather than grouped. This is then a form of regression analysis, where curves representing the mean and SD are fitted to the data plotted against age, and several iterative methods have been proposed for this.[30−33] Again the two curves can be plugged into Eq. (14.1) to provide the required centile curves.

Distributional assumptions

The previous section assumes that the data are normally distributed and hence summarized by the mean and SD. Usually this applies to measurements with relatively low variability, such as height or head circumference, where the coefficient of variation (CV) is less than 0.05 or 5%. But other more variable measurements, e.g. weight or skinfold thickness where the CV is 10−20%, have distributions with some degree of right skewness. Here the assumption of normality does not hold and a different approach is needed.

It is possible to obtain the centiles for such measurements empirically, i.e. without making any distributional assumptions, by sorting the data into order and estimating the required centiles as smooth curves – this is known as "quantile regression."[34] But there are two major disadvantages of quantile regression for estimating centile curves: (a) the curves may touch or even in extreme cases cross, and (b) they don't allow measurements to be converted to SD scores.

Another way to handle skewness is to transform the data to bring the distribution close to normal, a common transformation being the Box-Cox power.[35] This introduces a third parameter, in addition to the mean and SD, to compensate for skewness in the distribution at each age. The value of the parameter may be constant (e.g. transforming all the data to logarithms), or it may change with age like the mean and SD.

The concept of an age-varying adjustment for skewness was first proposed by Van't Hof et al.,[36] and extended and formalized by Cole.[37] Based on the Box-Cox transformation Cole called the process the LMS method, the three letters L-M-S representing respectively λ the Box-Cox power, μ the median and σ the CV. The median is estimated from the mean on the transformed scale, where the distribution is symmetric as the skewness has been adjusted for by the transformation. The CV is preferred to the SD because the SD – like the mean – tends to increase with age, whereas the CV is more constant through childhood, and indeed is often similar in infancy and adulthood. The quantities λ, μ and σ have corresponding smooth curves plotted against age, estimated by maximum likelihood, and these *L, M* and *S* curves together define any required centile curve using the equation

$$Centile_{100\alpha} = M(1 + LSz_\alpha)^{1/L} \tag{14.2}$$

where as before z_α is the normal equivalent deviate corresponding to the required centile. Substituting $L = 1$ which corresponds to the normal distribution gives the simpler formula

$$Centile_{100\alpha} = M(1 + Sz_\alpha) = M + MSz_\alpha$$

which, bearing in mind that *M* is the mean, *S* the CV and *MS* the standard deviation, is the same as Eq. (14.1).

An immediate spin-off of this approach is that skew data, in addition to those that are normally distributed, can be expressed as SD scores simply by rearranging (Eq. 14.2):

$$z = \frac{\left(\frac{Measurement}{M}\right)^L - 1}{LS}. \tag{14.3}$$

Setting $L = 1$ in Eq. (14.3) gives the formula

$$z = \frac{\left(\frac{Measurement}{M}\right) - 1}{S} = \frac{Measurement - M}{MS}$$

which is the usual formula for calculating the SD score. This ability to express measurements as SD scores, irrespective of whether or not they come from a skew distribution, leads to substantial simplifications in the analysis of anthropometry data (see later). We have already seen its value for optimally designing growth studies.[19]

Cole and Green later extended the LMS method to continuous age.[38] Subsequently Rigby and Stasinopoulos generalized it as GAMLSS (generalized additive models of location, scale and shape) which includes adjustment for kurtosis (in addition to skewness) and a choice of error distributions.[39] The LMS method is called BCCG (Box-Cox Cole Green) in GAMLSS, while kurtosis models based on the t and power exponential distributions are called BCT and BCPE respectively.

The WHO growth standard was constructed using GAMLSS, which was chosen after an exhaustive comparison of all the available methods.[40] In practice the models fitted to the WHO curves were based on the BCCG family, and so were equivalent to the LMS method.[38]

Form of smoothing

The simplest form of curve to use for smoothing data is a low order polynomial in age, e.g. a linear, quadratic or cubic curve. The polynomial is easy to fit using regression analysis, and the regression coefficients provide a parsimonious summary of the fitted curve. But the substantial disadvantage of polynomials, particularly higher order polynomials applied to data with complex age trends, is that they behave poorly at the extremes of the data. Edge effects mean that the polynomial is often a poor fit at the youngest and oldest ages, and the curve may be unacceptably "wiggly" in between.

Fractional polynomials[41] largely avoid these problems. The conventional polynomial, containing terms with successive integer powers of age (t, t^2, t^3 etc) is replaced by an equation with selected powers of age, the set of permissible powers being integer powers in the range -2 to $+3$ and certain non-integral or zero powers, for example $\sqrt{t}$ or $\log(t)$. As an example the growth curve described by Earl Count[42] 80 years ago is a fractional polynomial:

$$Y(t) = \beta_0 + \beta_1 \ \mathrm{t} + \beta_2 \log(t)$$

Fractional polynomials are effective at modeling the shapes of curves where both the curve and its slope either increase or decrease monotonically, as happens with anthropometry during gestation and in the pre-school period. But they are less useful over longer periods of time, where either the measurement or its velocity changes non-monotonically with age. Height in childhood and adolescence, or body mass index during childhood, are two examples where fractional polynomials are insufficiently flexible to model the underlying trends – height because of the pubertal growth spurt and body mass index because of the rise then fall then second rise in early life.[43]

Tailor-made parametric growth curves have been developed for certain measurements, e.g. the Jenss-Bayley curve for weight or length in infancy,[44] the Preece-Baines curve for height in puberty,[45] or the JPA-2 curve for height from birth to adult.[46] In general they are parsimonious (with between 4 and 8 parameters to be estimated) and provide a good fit to the data. As such they are useful functions to estimate the mean or median curves described in the previous section.

But these special parametric growth curves are not available for all measurements, and in any case they are not well suited to modeling age-related trends in say the SD or the skewness, except in very simple cases. For this a more flexible approach is needed.

Spline smoothing and kernel smoothing are two related techniques that have proved effective for fitting smooth curves to data. They are both forms of local moving averages of the data, where the range of data averaged at each age (bandwidth) and the weightings applied to the data (weighting function) are varied in different ways.[47,48]

Kernel regression has generally been applied to quantile regression,[49–52] while the LMS method uses natural smoothing splines.[38] The penalized B-splines or P-splines of Eilers and Marx[53] work particularly well in GAMLSS, and they include variants that provide for example a monotonic spline curve, which is useful for measurements like height that plateau in adulthood.

Available software

Most of the techniques described here can, with more or less effort, be fitted with standard software, e.g. Stata, SAS or *R*. The *gamlss* package in *R* is a powerful tool for fitting a wide range of semiparametric GAMLSS models,[39] including the LMS method as a special case. Royston has provided Stata do-files to fit the shifted log, Box-Cox and exponential transforms with fractional polynomials. The author's *sitar* package in *R* includes several functions useful for designing, analyzing and plotting growth references.[54]

Variants of the distance chart

The discussion so far has focused on the simplest form of distance chart. But other forms of chart based on the distance chart also deserve a mention.

Puberty

Puberty is a time when children of the same age can differ dramatically in size, due to differences in their stage of maturation.[55] In principle this could be represented on a chart with an extra scale for stage of maturation, but it would need to be plotted in three

dimensions. As a compromise, a modified version of the distance chart has been developed that partially addresses this issue.

Variability in the timing of puberty causes the median curve on the distance chart to be flattened relative to the growth curve of individual children.[15,56] The slope of the median curve at its steepest, which represents the measurement's peak velocity, is biased downwards, i.e. it is less than the peak velocity in individual children. There are broadly two ways to respond to the bias – ignore it or adjust for it.

Tanner and Whitehouse[57] minimized it by modifying the shape of the height centile curve during puberty. They drew it as steeper than it actually was, so that instead of representing the median height at each age, it followed the growth curve of a hypothetical child of average height, average peak height velocity and average age at peak height velocity. They called it a tempo-conditional chart, and its advantage was said to be that it minimized centile crossing as the median curve is similar in shape to a growth curve.

In practice it does not eliminate centile crossing. Any child whose height distance, peak velocity or age at peak velocity is not average will cross centiles at some point during puberty. The one advantage of the tempo-conditional chart over the conventional chart is that its median curve looks more like a growth curve. Its disadvantage is that the "median" curve no longer represents the population median height in puberty, and similarly the other "centile" curves do not correspond to the population centiles.

The alternative approach to the bias is to ignore it, which is what the conventional distance chart does. The centile curves provide unbiased estimates of the distribution centiles at all ages including puberty, and in addition the age when the median curve is steepest is an unbiased estimate of the mean age at peak velocity. However mean peak velocity is underestimated.[15]

Neither approach satisfactorily solves the problem of assessing both distance and velocity in puberty. Opinion is divided as to which approach is better, and ultimately the choice will depend on the context where the assessment is made.

Repeated measures

The distance chart is usually based on data where each subject provides one measurement. But often the study design includes longitudinal or mixed longitudinal data and participants have more than one measurement. The question then is – what to do with them? There are three schools of thought: (a) restrict the data to one measurement per subject (the first or a random choice), (b) use the mean value for each subject, or (c) use all the data for each subject and treat them as unrelated.

The first alternative is safe but conservative – it ensures that there are no repeated measures but it also wastes data. The second approach is not correct, as it introduces differential weighting. The variability of the mean of several points is smaller than for a single point, so the measurement error for subjects with averaged repeated measures is artificially reduced.

The third alternative, to retain all the data, is probably the best. The issue comes back to distance versus velocity, in that a distance chart contains no information about velocity. The distance centile curves can be thought of as a series of snapshots of the measurement distribution at different ages, smoothly joined across ages. Each such snapshot is unrelated to the others, so it does not matter if a subject is represented in more than one snapshot – the shapes of the centiles are not affected.

What *is* affected is the precision with which the centile curves are calculated. Consider an extreme example, two surveys each with 1000 points, one a longitudinal study of 50 subjects measured annually from 0 to 20 years, the other a cross-sectional survey of 1000 children with ages uniformly distributed between 0 and 20 years. If the two sets of subjects are drawn randomly from the same reference population, then on average the two sets of fitted centiles will be the same – both will be unbiased estimates of the population centiles. The longitudinal centiles will be far less *precise*, in that the between-subject variability will be based on 50 subjects rather than 1000, and the confidence intervals for each centile will be wider, but the centile themselves will (on average) be the same. Wade and Ades[58] have argued the case more formally, showing that adjusting explicitly for the correlation between repeated measures does not materially alter the shapes of the fitted centiles.

This may appear counter-intuitive, but Healy[59] showed it to be *exactly* true for the analogous situation of paired organs in large samples. Here subjects provide two measurements (e.g. two arms or two ears), and Healy shows that the correct approach is to ignore the pairings and treat the data as independent.

In general, if the repeated measures data are balanced, i.e. every subject has measurements at the same ages (as would be the case in a longitudinal study with no missing data), then the repeated measures structure can be ignored for the purposes of constructing a distance chart. If some of the data are missing, then so long as they are missing at random the repeated measures structure can be ignored.

Visualizing the curves

This section shows what typical growth charts look like, and how their structure depends on the underlying LMS curves.

Centile growth charts

Fig. 14.1 illustrates the British 1990 reference centiles from birth to 21 years by sex for weight, height, body mass index and head circumference.[13] They were constructed using the LMS method and are shown in nine-centile format. The reference is now old, but the centile curves for the different measurements tend to be relatively invariant in shape over time, even though the actual values change. This can be seen by comparing them with more recent references such as those for Flemish[60] and Norwegian children.[61]

The weight and height charts clearly show the growth spurt in puberty, when the centiles are steeper than earlier or later. In contrast the BMI centiles show no such spurt, as the weight and height spurts cancel each other out. The height and particularly the head circumference centiles are much closer together than for weight or BMI, reflecting the smaller CV.

LMS curves

The shapes of the centiles depend on the shapes of the *L*, *M* and *S* curves, which define the first three moments of the distribution by age. This also applies to the GAMLSS BCT

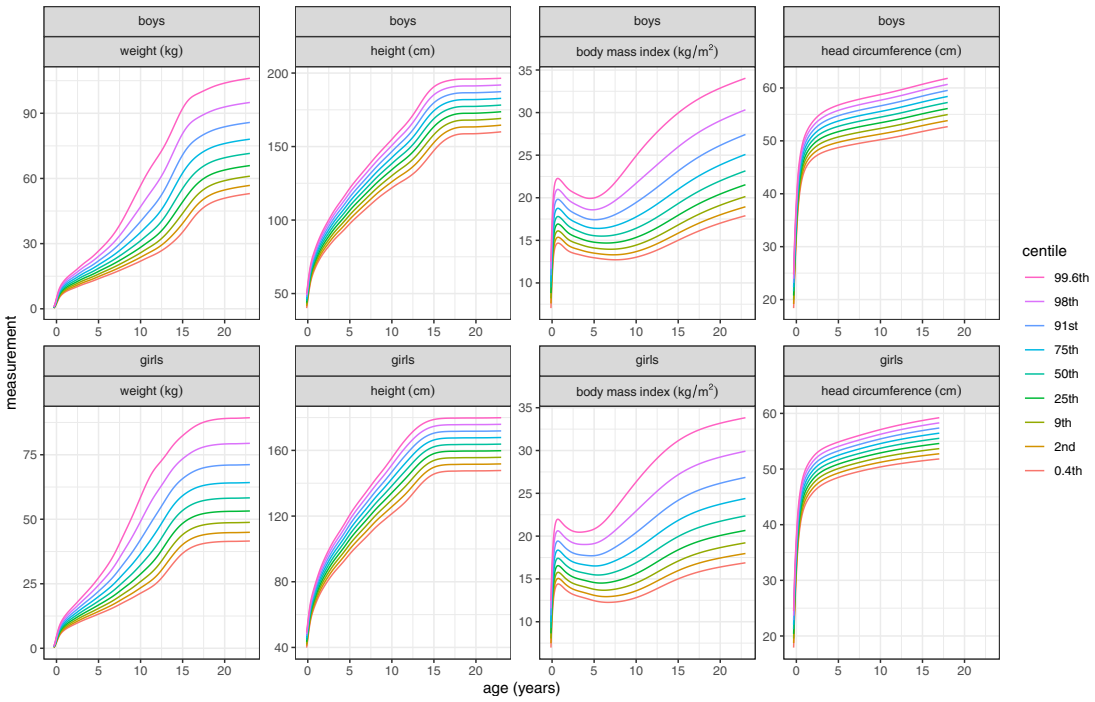

Fig. 14.1

Centiles for weight, height, body mass index and head circumference by sex in the British 1990 growth reference.[5] The nine centiles are spaced two-thirds of an SD score apart.

and BCPE models, which have in addition a curve for kurtosis. The curves provide useful information about the growth processes underlying the measurement. Fig. 14.2 shows the *L, M* and *S* curves by sex for the centiles in Fig. 14.1, with the measurements by row and the LMS curves by column. The *M* curve medians are all familiar in shape, but it is instructive to compare them by sex. Prior to puberty girls are slightly shorter and lighter than boys, but they enter puberty earlier and are briefly taller and heavier, before the boys overtake them again. The pubertal growth spurt is visible for both weight and height, when the median curve is at its steepest, while there is no obvious pubertal growth spurt for BMI or head circumference.

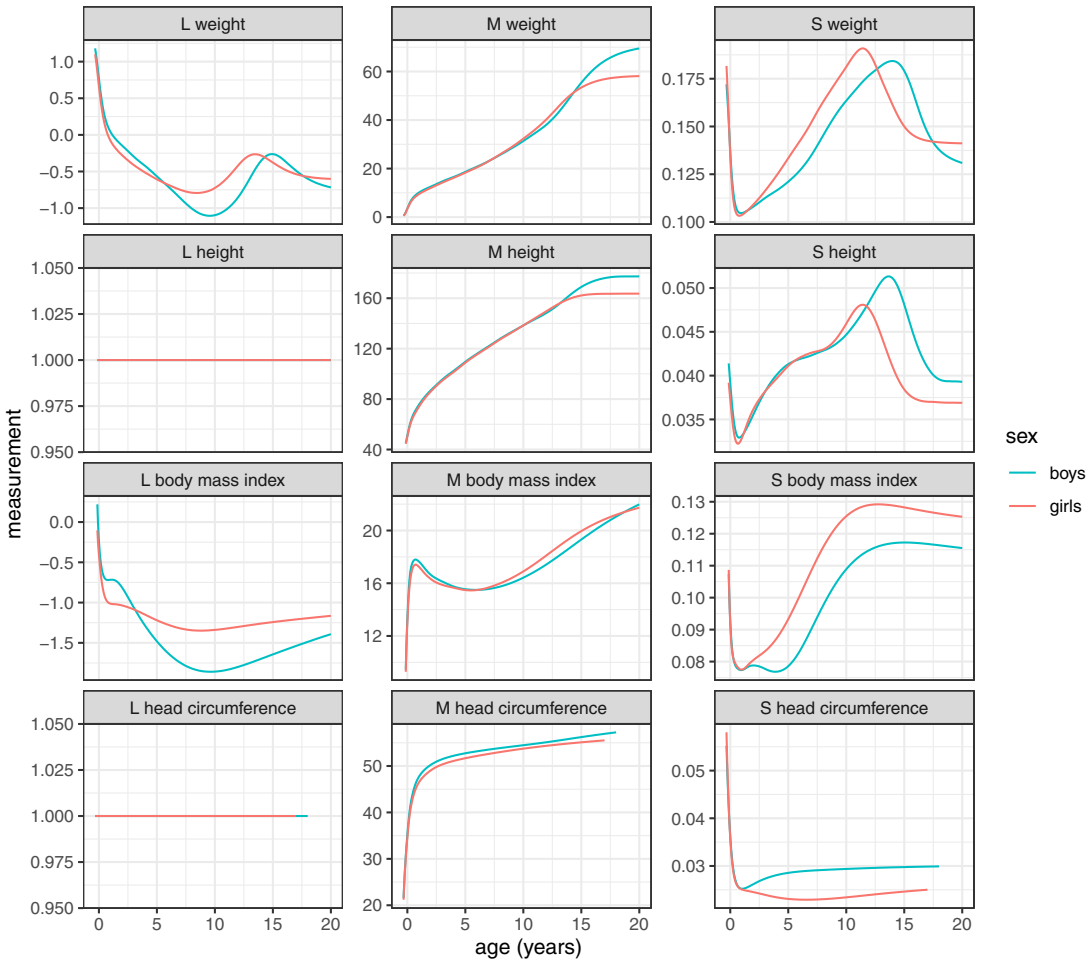

Fig. 14.2

L, M and S curves for the measurement centiles in Fig. 14.1 by sex in the British 1990 growth reference.[5] See text for details.

In Fig. 14.2 the *S* curves for CV in the four measurements all fall sharply immediately after birth, and reach a minimum at around 9 months of age. This is driven by centile crossing which has the effect of reducing the variability – it represents infants shifting from their birth centile to their preferred growth centile.[62] For weight and height the CVs then rise steeply until puberty, peak, and fall again to values near those seen at birth. The peak occurs two years earlier for girls than boys, reflecting puberty timing. The rise in variability until puberty represents heterogeneity in the rate of maturation, so that individual growth curves differ in slope and diverge progressively until puberty. Then as growth slows the variability falls again.

For BMI the CV also rises until puberty, but unlike with weight and height the CV remains high in adulthood. For head circumference the CV is low – below 3% – throughout childhood.

Fig. 14.2 also shows the *L* curves for Box-Cox power. The distributions of height and head circumference are close to normal so *L* is set to 1. But for weight and BMI the distributions are appreciably skew, and for weight the skewness changes appreciably with age. Note that the slope of the weight *L* curve is steepest at ages 12 and 14 in the two sexes, i.e. the ages when the *M* curves are steepest and the *S* curves are at a peak. So all three curves are affected by the timing of the pubertal growth spurt.[15]

These insights into the underlying growth processes are in addition to the practical value of the charts they define.

Multiple measurement SD score charts

When multiple measurements are available for assessment they each require their own chart, and multiple charts make the assessment more complicated. An alternative approach is to first convert the measurements to SD scores, as is easily done by computer, and then plot the SD scores against age. This puts all the measurements onto the same SD score scale, and it allows them to be plotted on just one chart. Different symbols can be used to distinguish between the measurements, and points can be joined up over time in the usual way.

Centile curves on the SD score chart are very simple in shape, consisting of horizontal straight lines. The growth curves of individuals are also more linear when plotted in SD score units. Overall the SD score chart allows a considerable amount of information to be displayed in a compact way. As an idea it is far from new, dating back to 1989,[63] but in the computer era it provides a useful alternative form of presentation for multiple measurements.

Charting velocity

The distance chart treats repeated measures data as unrelated, so how is velocity to be assessed?

Unconditional velocity

Traditionally growth velocity has been measured in the original units of measurement, e.g. cm/year for height velocity, which leads to a velocity chart where the centile curves highlight the pubertal growth spurt.[64] The velocity chart is constructed in the same way as the distance chart except that paired data are needed to calculate each subject's velocity. In addition the time gap between measurement pairs needs to be standardized, e.g. 1 year for height, as this affects the variability of the velocity. Puberty affects the velocity chart just as it does the distance chart, and Tanner and Whitehouse produced tempo-conditional velocity charts to match their distance charts.[57]

However there are disadvantages with using velocity charts in clinical practice. The velocities have to be calculated for each child, and the measurements and velocities have to be plotted on two charts. Computers make this easy, but having two charts rather than one does complicate the assessment.

An alternative is to focus on centile crossing. Velocity, relative to average velocity for age, is effectively centile crossing, so it is logical to measure velocity in centile units. Statistically SD scores are more appropriate than centiles (as the SD score scale is not bounded at 0 and 100), so the velocity can be expressed as the rate of change in the SD score. A child whose centile (and hence SD score) remains constant over time (i.e. no centile crossing) has zero rate of change, and this corresponds to the median velocity.

Measuring velocity on the SD score scale has two benefits: the change in SD score can be assessed directly, and the corresponding velocity can be represented visually on the distance chart. To express centile crossing as a velocity centile, the variability of centile crossing needs to be known. This comes directly from the standard deviation of the change in SD score, which surprisingly does not involve the time interval between measurements – it depends only on the correlation r between SD scores at the two ages of measurement. The actual formula is:

$$\text{SD of SD score change} = \sqrt{2(1-r)}. \tag{14.4}$$

Take for example weight from birth to 1 year. The correlation between weight SD scores at birth and 1 year is 0.59,[65] so the SD of the SD score change from birth to 1 year is:

$$\sqrt{2(1-0.59)} = \sqrt{2 \times 0.41} = \sqrt{0.82} = 0.91.$$

The mean change in SD score over the year is 0, and 95% of infants are within ±2 SDs of this, i.e. changes in the range −1.8 to +1.8 SD score units. Hence many infants cross centiles by up to 1.8 Z-score units during their first year, e.g. between the median and the third centile, which emphasizes how extreme centile crossing can be in early life.

The same information can be used to express an individual infant's SD score change as a velocity centile. Take a child whose weight is on the 16th centile at birth (SD score = −1), but who has caught up to the median by 1 year − this upward centile crossing is an increase of 1 SD score unit. A change in SD score of +1 corresponds to +1/0.91 = +1.1 SDs, corresponding to the 86th centile for SD score change, or equivalently the 86th velocity centile (assuming velocity is normally distributed). So this child has grown faster over the first year than 86% of infants born on the 16th centile.

Conditional velocity

Eq. (14.4) is a logical way to assess centile change. However there is a complication due to the statistical phenomenon of regression to the mean. This states that on average, the centiles of individuals (or groups of individuals) followed over time tend to become less extreme, more ordinary, closer to the median. This is because there is a built-in negative correlation between the starting centile and the change in centile over time − a child on a low starting centile on average crosses centiles upwards (i.e. exhibits catch-up growth), whereas the opposite occurs for a child starting on a high centile.

To adjust velocity for regression to the mean, the SD score on the second occasion is compared with that predicted from the first occasion. The prediction comes from linear regression analysis:

$$z_2 = r \times z_1. \tag{14.5}$$

So instead of the change in SD score over time, e.g. $z_2 - z_1$, the adjusted change is used, $z_2 - r \times z_1$, where again r is the correlation between z_1 and z_2. The SD of this adjusted SD score change is $\sqrt{1 - r^2}$, slightly smaller than Eq. (14.4).

This form of velocity is known as *conditional* velocity, i.e. conditional on the previous measurement. Velocity as defined in the previous section is by analogy called *unconditional* velocity.

In the example above, where the SD score increases from −1 to 0 over the first year, the adjusted increase in SD score is

$$z_2 - r \times z_1 = 0 - 0.59 \times (-1) = 0.59$$

which is appreciably less than the unadjusted increase of 1 unit. The corresponding SD for velocity is $\sqrt{1 - 0.59^2} = 0.81$, so the velocity SD score is $0.59/0.81 = 0.73$, which corresponds to the 76th velocity centile. So this low birthweight infant would be expected to show some catch-up, and adjusting for it puts her velocity at the 76th rather than the 86th centile.

This process can be reversed to define the velocity as an SD score based on the two measurement SD scores. It is useful for representing velocity on the distance chart. Consider two SD scores, z_1 at age t_1 and z_2 at age t_2, where the correlation between them is r. Also, call the velocity SD score z_v. Then the following relationship holds:

$$z_2 = r \times z_1 + \sqrt{1 - r^2} \times z_v. \tag{14.6}$$

Now convert z_1 and z_2 to measurements, plot them on the chart at ages t_1 and t_2, and join the two points. The slope of this line is the velocity, and we know from Eq. (14.6) that its velocity SD score is z_v. In this way we can draw a line on the distance chart whose slope corresponds to a particular velocity centile.

A child's velocity is assessed on the chart by comparing the slope of her growth curve with the slope of the reference velocity line on the chart at that age. If the two lines are parallel then her velocity is equal to the nominal velocity centile. If her line is steeper she is above the centile, while if shallower she is below it.

In practice velocity centiles – like distance centiles – change with age, so the line needs to be a curve with age-varying slope. And several such curves are needed, so that when the child's data are plotted on the chart there is a nearby curve to compare its slope with. These conditional velocity curves are called *thrive lines,* as they can assess failure to thrive.

The thrive lines cut across the distance centiles, and their slopes (*not* their positions) indicate the velocity centiles at each age. Velocity centiles below the 50th cross distance centiles downwards, and those above the 50th cross upwards. The details of how to construct the curves are given elsewhere.[66]

Fig. 14.3 illustrates the principle with the WHO girls infant weight chart, along with an example growth curve that is discussed later. Fig. 14.3A shows the nine weight centiles, while B shows thrive lines for the 5th weight velocity centile measured over a 1-month period, with the distance centiles retained in the background. The thrive lines all cross centiles downwards, indicating the slope of weight curves growing on the fifth velocity centile.

Fig. 14.3C shows thrive lines for the 95th velocity centile over a 1-month period, which cross centiles upwards reflecting rapid weight gain. Note that in general the slopes of the thrive lines depend on both age and weight, which means that the curves are not parallel to each other. As a reminder to the user that velocity in 3B and 3C is based on 1-month intervals, the thrive lines are drawn as a series of 1-month segments.

Now consider the example growth curve., which crosses centiles downwards to 2 months and then upwards until 9 months (see Fig. 14.3A). But this gives no clue as to how unusual the growth pattern is. The growth curve consists of monthly weights, so weight velocity can be assessed using the 1-month thrive lines in Fig. 14.3B and C. At age

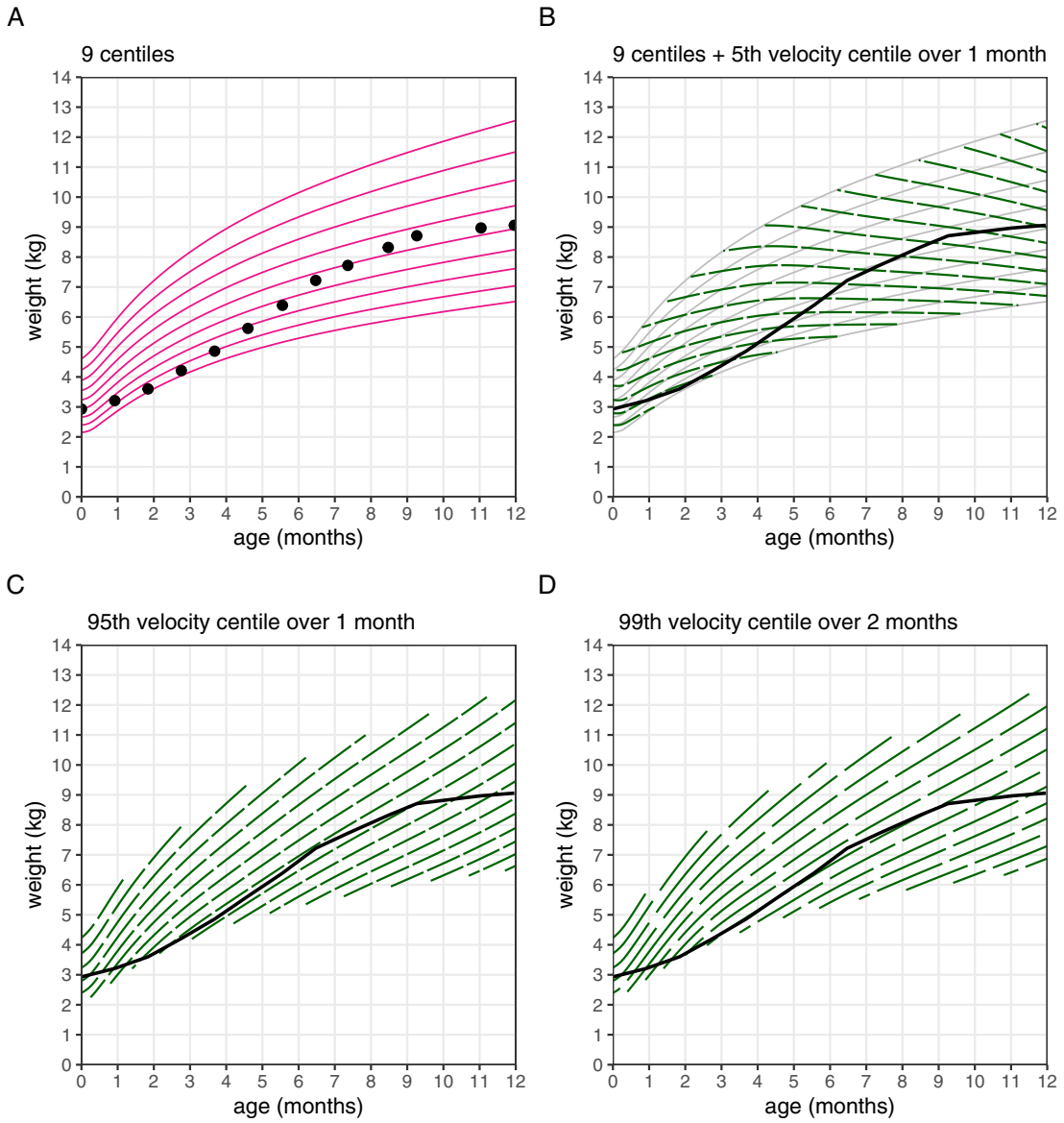

Fig. 14.3

Weight centiles and thrive lines for infant girls based on the WHO growth standard. (A) nine centiles spaced two-thirds of an SD score apart; (B) centiles plus thrive lines for the fifth weight velocity centile measured over a 1-month period; (C) thrive lines for the 95th weight velocity centile measured over a 1-month period; (D) thrive lines for the 99th weight velocity centile measured over a 2-month period. The slope of the line joining an infant's successive weights over a 1- or 2-month interval is compared with the slope of the nearest thrive line. See text for details.

1 month the curve crosses the thrive line in Fig. 14.3B downwards, which indicates that weight velocity is below the fifth centile at this age. Conversely from 3 to 6 months the curve runs parallel to the thrive lines in Fig. 14.3C, indicating weight velocity on the 95th centile.

But the fact that the growth curve maintains this unusually high velocity over several months means that the velocity over the longer period is even more extreme. Fig. 14.3D demonstrates this with thrive lines for the 99th velocity centile over 2-month intervals, where again the growth curve tracks the thrive lines. The more extreme centile and the longer interval have opposite effects on the thrive lines, so that they are effectively unchanged in shape from Fig. 14.3C to D. They indicate an unusually steep pattern of catch-up growth. Calculating weight velocity for the whole period from 3 to 9 months shows it to be on the 99.9th centile, i.e. almost off the scale. This is a most unusual growth pattern.

Adding thrive lines to the chart centiles can make the chart appear cluttered, as seen in Fig. 14.3B, which rules it out for paper charts unless the thrive lines are added as a transparent overlay.[66] However displaying the data on a computer screen would with suitable software allow one to select the background as centiles and/or thrive lines as required.

Conditional references

Conditional velocity is just one example of the family of conditional references. Eq. (14.5) shows how one SD score is predicted from another, where the two SD scores correspond to consecutive measurements in one child. But the meanings of the two SD scores are quite general — they could for example be birthweights for two siblings, giving a reference of birthweight conditional on sibling birthweight, or heights of parent and child, i.e. a reference of height conditional on parental height. By specifying the reference on the SD score scale the only extra information required for the reference is the correlation between the pairs of measurements.

Designing and printing the chart

The final stage in the production of a growth reference is to design, print and distribute the charts. As with any other marketable commodity it pays to design the chart to suit its users, and extensive consultation is needed to ensure that the format of the chart is optimal. This involves issues to do with the choice of centiles on the chart (as discussed earlier), the age ranges and combinations of different measurements to include in particular charts (for example weight, length and head circumference on a single chart in the first year), the choice of age scale (e.g. decimal or in weeks or months for the first

year), and the chart's general appearance in terms of orientation (portrait or landscape), color scheme, line types, labeling, scales and gridlines. They make a substantial difference to the usability of the chart in clinical practice.

Remember that different users, e.g. endocrinologists versus community paediatricians versus health visitors, will use the charts in different ways, so it is important to canvass opinion as widely as possible before settling on the final design. And providing some forum for feedback can ensure that later printings of the charts incorporate modifications to improve them further. As an example, the UK-WHO charts were the outcome of an extensive design process involving an expert group working with graphic designers, and incorporating feedback from several rounds of focus groups.[6]

When to replace

Once charts have been available for a period of time, the question arises: should they be updated? Due to secular trends in growth, children change in size and/or shape after the chart is produced. Updating the chart ensures that the centiles continue to reflect accurately the proportions of children outside the extreme centiles. An interval of 10–15 years between updates is typical, e.g. the Dutch national growth surveys took place in 1955, 1965, 1980, 1997 and most recently 2008. But there are two disadvantages to updating charts that also need to be borne in mind.

First, it takes a very long time for a new chart to displace the old. This is due partly to ignorance (the new chart is not widely known about), partly to inertia ("I prefer chart I'm used to"), and partly to finance (purchasing officers expect existing stocks of charts to be exhausted before ordering new ones).

The second disadvantage is more subtle: the secular trend may be toward less optimal growth, e.g. the recent increase in obesity that has shifted weight and body mass index centiles upwards. If the centiles are used to define overweight, e.g. the 91st centile on the body mass index chart,[43] then this provides a nominal prevalence of 9% overweight. Such a prevalence was appropriate at the time the chart data were collected (1990), but with the trend to increasing fatness the prevalence has since increased. If the chart were to be updated and the 91st centile shifted upwards the prevalence of overweight would revert to 9%, but it would not be comparable with the 9% prevalence on the previous chart – the prevalence rates before and after would not be comparable.

For this reason the British body mass index chart has been "frozen" in time and will not be updated.[67] In effect the chart has become a standard rather than a reference – it reflects body mass index at an earlier time when the population was less fat than it is now.

Electronic growth charts

In recent years there has been a major shift towards providing growth charts electronically rather than on paper. The child's measurements are input by keyboard directly into the child's electronic patient record, and software can then draw the growth chart with the child's measurements on the computer screen. Compared to the traditional approach this has many advantages—paper charts are immediately redundant, the process of plotting and any associated plotting errors are avoided, the data are recorded automatically, and extra information can be added to the chart such as z-scores or thrive lines. In addition the chart can be updated centrally as and when the need arises.

The UK Royal College of Paediatrics and Child Health has produced an open source application programming interface (API) at https://growth.rcpch.ac.uk/ which allows software developers to submit anthropometry to the API and it returns the corresponding z-scores, and also optionally plots the data on a screen chart. The advantage of the API is that developers do not need any special skills to handle the data or plot the chart, it acts as an expert "black box".

In addition, being open source and hence publicly available, the code is in effect peer reviewed on a continuous basis - users can submit improvements to the software to be vetted for inclusion in the API. The development of the API represents an important step forward in simplifying and improving the assessment of child growth.

Conclusions

The process of producing new growth charts involves several important stages. The choice of reference population and sample, collecting and recording the anthropometry, analyzing the data and designing and printing the chart, together require the skills of specialists in many different areas. The outcome should be a set of charts that are effective in recording and assessing the growth of the children they serve.

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Internet resources

There are several websites with free resources for growth assessment, some general and some dedicated to particular growth references. A few are given here.

RCPCH Digital Growth Charts API. to help developers manipulate growth data: https://growth.rcpch.ac.uk/.
GAMLSS, an R package for fitting growth reference centiles to data: https://cran.r-project.org/package=gamlss.
LMSgrowth, Excel add-in software for analysing growth data with references based on the LMS method: https://www.healthforallchildren.com/product-category/shop/software/.
UK-WHO charts, information, instructions and training materials: http://www.growthcharts.rcpch.ac.uk/.
US CDC 2000 charts, data tables, educational materials, reports: http://www.cdc.gov/growthcharts/.
WHO charts, data tables, training, publications, WHO Anthro software: http://www.who.int/childgrowth/en/.

Special topics

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CHAPTER 15

Evolution of human growth

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Introduction: evolution of human maturation

Human growth and maturation in evolutionary perspective

An evolutionary approach to human growth studies relies upon comparison between modern humans (*Homo sapiens*) and living primates, particularly chimpanzees (*Pan*). The common ancestry of *Pan* and *Homo* becomes a basis for evaluating similarities and differences in lengths of life stages, in features associated with each stage, and in the timing of development of body systems. Ape and human research that documents tooth and skeletal growth offers the opportunity for assessing maturational patterns of ancient human species.

In this chapter we first illustrate the methods and findings of nonhuman primate studies that shed light on life history and interpretations of maturity patterns in fossils. We focus on research that elucidates patterns in somatic features of ape and human species (for social behavioral development, see e.g. Pereira and Fairbanks[1]). We then summarize and review available examples of immature hominin fossils. Somatic information gleaned from living populations of apes and humans assists in interpretation, reconstruction, and modeling of hypotheses about the evolution of human maturation.

Anthropology: evolutionary approach

Life history and stages of life

In evolutionary anthropology studies, we view life history and the life course in two ways: (1) as a species signature; and (2) as individual life stages of its members. In the transition from one life stage to the next, birth ends gestation and begins infancy, weaning ends infant dependence and initiates juvenile independence; sexual maturity launches reproduction and adult life, and old age indicates a life near its end. Individual survival throughout immaturity determines whether the opportunity to reproduce arises in the adult

Human Growth and Development. https://doi.org/10.1016/B978-0-12-822652-0.00016-X

stage, a key component in the evolutionary process. Life history features have been shaped over evolutionary time and represent the adaptive potential for a species, that is, the particular sequence, cadence and timing to maturity. Anthropologists use a combination of somatic and behavioral markers to define each life stage and to illuminate the order of change during growth. Differences in life history features, and in pattern and timing of transitions from one stage into the next, reflect species' divergent evolutionary histories.

Early studies on immature primate life stages and development were carried out by anatomist and primatologist Adolph Schultz.[2–6] Schultz focused on skeletons from collections of wild-shot individuals, ranging widely across the primate spectrum: apes - gorillas, gibbons, orangutans, chimpanzees; and monkeys – colobus, proboscis, macaques and langurs. Schultz, a skilled artist, illustrated a comparative drawing that summarized his findings on life stages across taxa, from lemurs, monkeys, and apes to humans, which is now a classic image widely referenced in primate growth and development studies.[6] (Fig. 15.1).

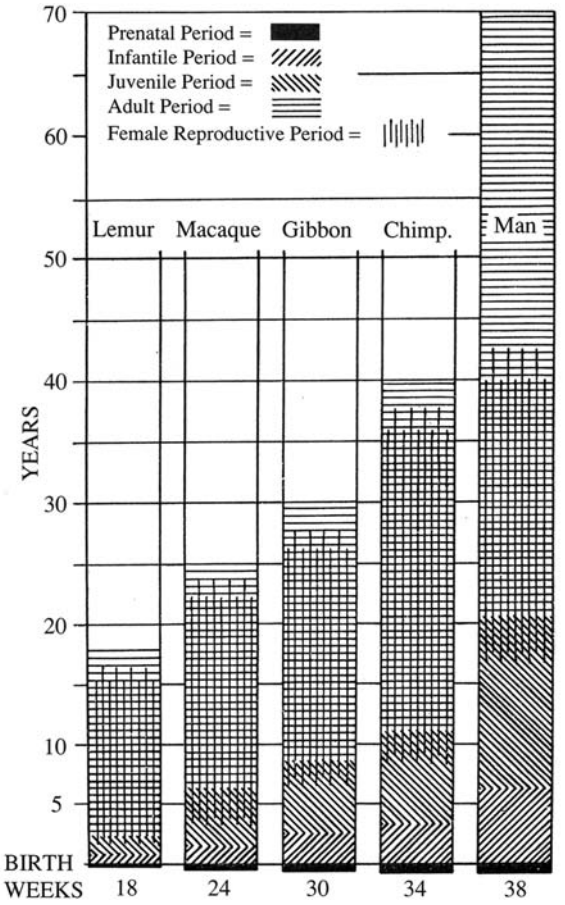


Fig. 15.1
Life stages in primates and humans, after Schultz[6].

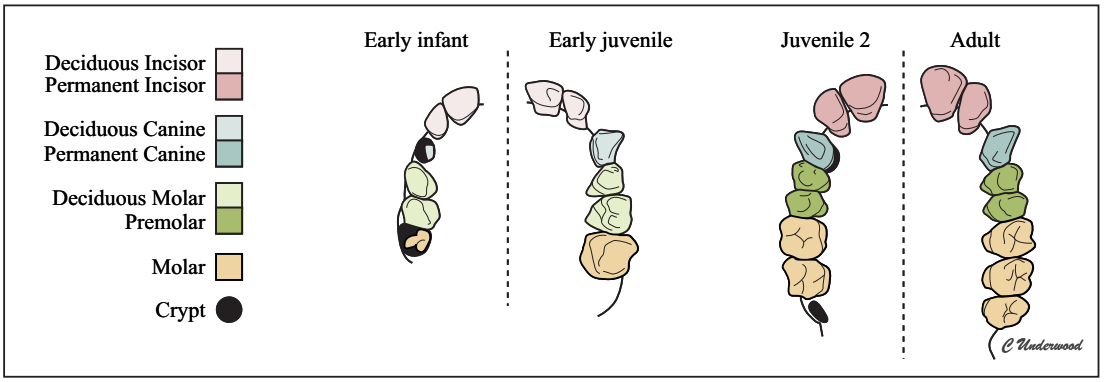


Fig. 15.2

Dental eruptions as a proxy for life stages in catarrhine primates. *Modified from Bolter DR, Zihlman AL. Primate growth and development: a functional and evolutionary approach. In: Bearder S, Campbell C, Fuentes A, McKinnon K, ed.* Primates in Perspective. *Oxford: Oxford University Press; 2011:408–422.*

Catarrhine monkeys and apes, including humans, have the same number and kinds of teeth (incisors, canines, premolars and molars) and broadly similar eruption patterns. Through dental analysis, Schultz proposed a way to compare life stages across species by identifying four dental stages: Infants - partial to full deciduous teeth erupted; Juvenile 1 - combination of deciduous and permanent teeth erupted; Juvenile 2 - only permanent teeth though not all are erupted; Adult - all permanent teeth in place.[3] Dental eruption stages became a proxy for behavioral markers of life history, for example, eruptions of the first permanent teeth (M1s) signaled an end of weaning, and eruptions of all permanent teeth indicated adulthood and reproductive life. cf. 7–9 (Fig. 15.2).

The extent of similarity among species depends upon how recently they shared a common ancestor. For example, compared to monkeys going back 22–24 million years, apes have a common ancestry with humans as recently as 4–5 million years ago; *Pan* and *Homo* share prolonged periods of immaturity, along with an increase in brain size, non-seasonality of births, and postponement of reproduction that includes a sterility phase as a sub-adult.[6,11,12] (Fig. 15.3).

When compared with African ape relatives, *H. sapiens* may have another life stage, "childhood." This life history phase follows infancy, postulated to extend the time that members of our species are dependent on other group members for food and travel, allowing for further somatic and behavioral development.[13–16] Overall, humans have potential for a long life, which is expressed in longer times spent in juvenility, in adolescence, and for females an extended post-reproductive phase. (Fig. 15.4).

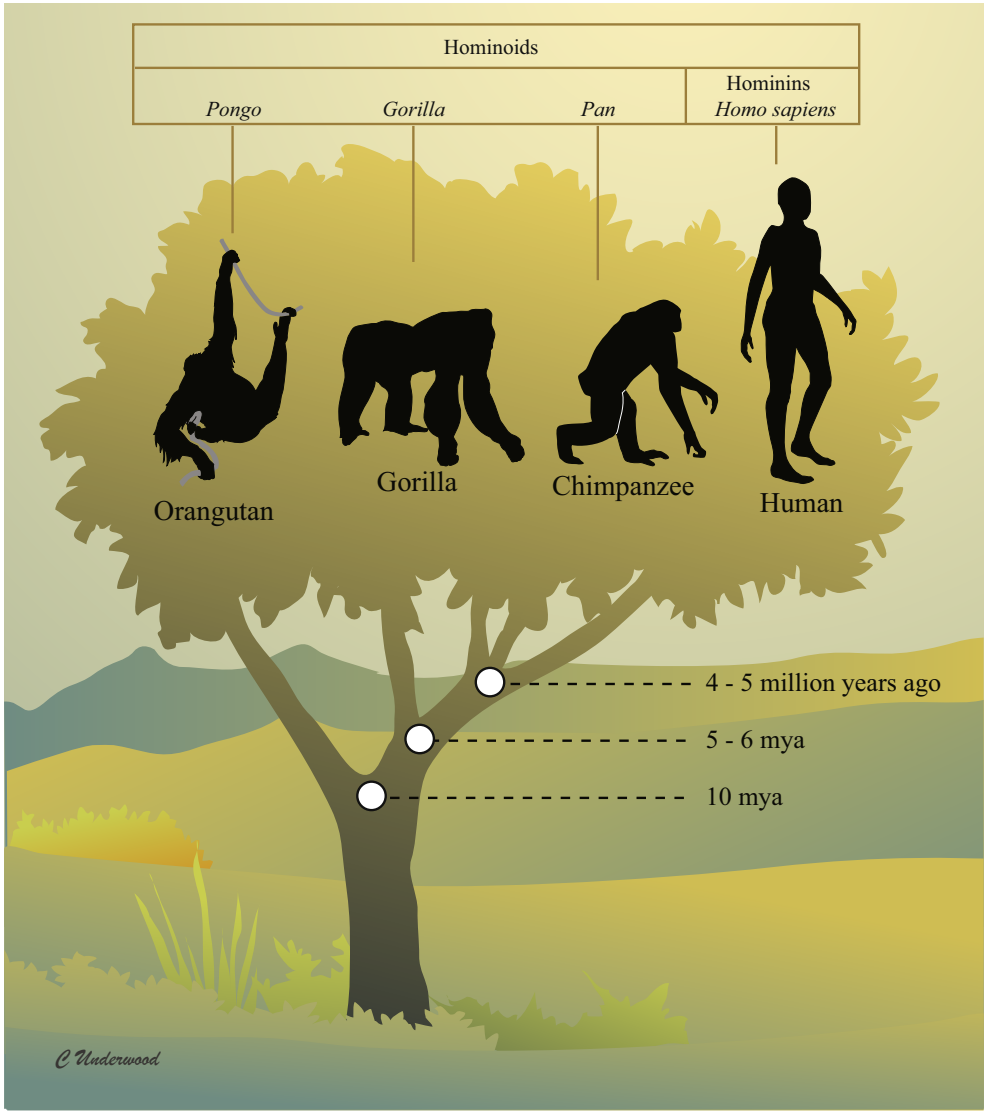
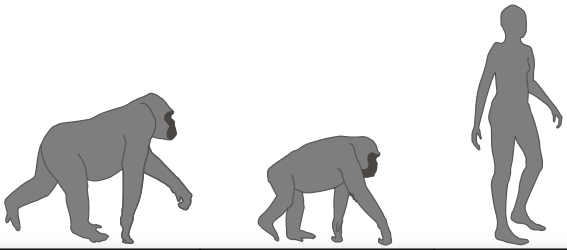


Fig. 15.3
Phylogenetic tree of great apes and humans. *Modified from Zihlman AL, Underwood CE.* Ape Anatomy and Evolution. *San Francisco: CreateSpace, Amazon; 2019.*

Contrast in methods

Methods for collecting information on growth in living apes and fossil humans depart from methods applied to studies on modern human growth. Human data are more abundant and have a velocity element to establish growth curves; sample sizes are



Life History Features*

	Gorilla[20-23] (eastern, western)	*Pan troglodytes*[24-27]	*Homo sapiens*[28-32]
Gestation length in days	258	226	~280
Age at weaning in years	4, 4.6	5	3 - 4
Age at M1 eruption[17-19] in years	3.8	4.0	5 - 7
First reproduction in years	10, 11	14	18 - 19
Birth interval (surviving young) in years	4, 5	5.7	3 - 4
Life span in years	40+	50+	60+
Female body wt in kg	95	30 - 40	48 - 60

* Information is derived from the sources listed; *Homo sapiens* data is compiled from modern foraging groups where available (ranges are only attempted for humans); see original sources.

C Underwood

Fig. 15.4

Life history features across African apes and humans. *Modified from Zihlman AL, Underwood CE.* Ape Anatomy and Evolution. *San Francisco: CreateSpace, Amazon; 2019.*

comparatively large. Individuals of known ages are followed during immaturity, through external body measurements, such as on height and weight, as well as on internal physiological changes.[33–35]

In contrast, the majority of early chimpanzee growth studies are cross-sectional and derive from relatively small numbers of captive individuals.[36–39] In those few exceptions where longitudinal data are available, an adolescent growth spurt has been detected in some

captive colony apes but the duration, timing and magnitude is variable, can be sexually dimorphic, and does not show the intensity seen in humans.[9,39–41]

Most primate studies have been carried out on provisioned, semi-sedentary primates that mature faster than their wild counterparts, so ages for timing of developmental events were systematically estimated to be younger than populations under naturalistic settings.[10,17,42–47] Long-term fieldwork on chimpanzees in the wild, of known age, has made possible the regular collection of their skeletons after death. This larger and more representative sample of immature chimpanzees and developmental events has resulted in revision of age estimates for the species.[11,17,45,48–51] Wild chimpanzees mature at a slower rate, thereby revising evolutionary models about the similarities and differences in maturational events in fossil and modern humans compared to the African apes.

For example, in Fig. 15.5 two wild juvenile female chimpanzees, an 8-year-old and a 12-year-old, show dental eruption timing and cadence of skeletal fusion sequences. The 8-year-old has newly emerged second molars (M2s), along with a combination of deciduous teeth of the lateral incisors, all canines and deciduous molars, and permanent medial incisors and M1s.[45,47] (See also Fig. 15.2). Skeletally she has no fusion at any of the long bone epiphyses or the acetabulum. She is immature dentally and skeletally, at the developmental stage comparable to a captive 6-year-old chimpanzee.

From the same population an older 12-year-old juvenile female has all permanent teeth emerged except the third molars (M3s) and no deciduous teeth remaining. Skeletally she has a mature hip joint seen in the complete skeletal fusion of the ilium, ischium and pubis bones at the acetabulum and fused elements of the proximal femur, indicating a more advanced stage of growth than the 8-year-old. However, her long bones and corresponding joints of the wrist, shoulder, and ankle are unfused, and growth is continuing. Only the elbow and hip joint elements have completed their growth, at the developmental stage comparable to a captive 9–10 year old chimpanzee.

Additional body features have been researched in primate growth studies, such as body mass and cranial capacity. A study on African vervet monkeys combined cross-sectional data of measurements taken in the field (e.g. body mass, trunk length, individual muscle and testes weights) with measurements taken in the lab – tooth eruption, long bone length, skeletal fusion, and cranial capacity (proxy for brain volume).[52] This collection from a wild population consists of 63 members including both sexes and all ages. The results documented for these combined measurements record a mosaic of timing when each component reached maturity.[10] (Fig. 15.6). For example, brain growth reaches maturity early in life, coinciding with M1 eruption, whereas body mass is late; in males it occurs after tooth eruption and fused long bones. The African monkey example parallels the findings of R.E. Scammon's human growth studies that document separate growth curves of body systems and tissues that peak at different times (1930).[53]

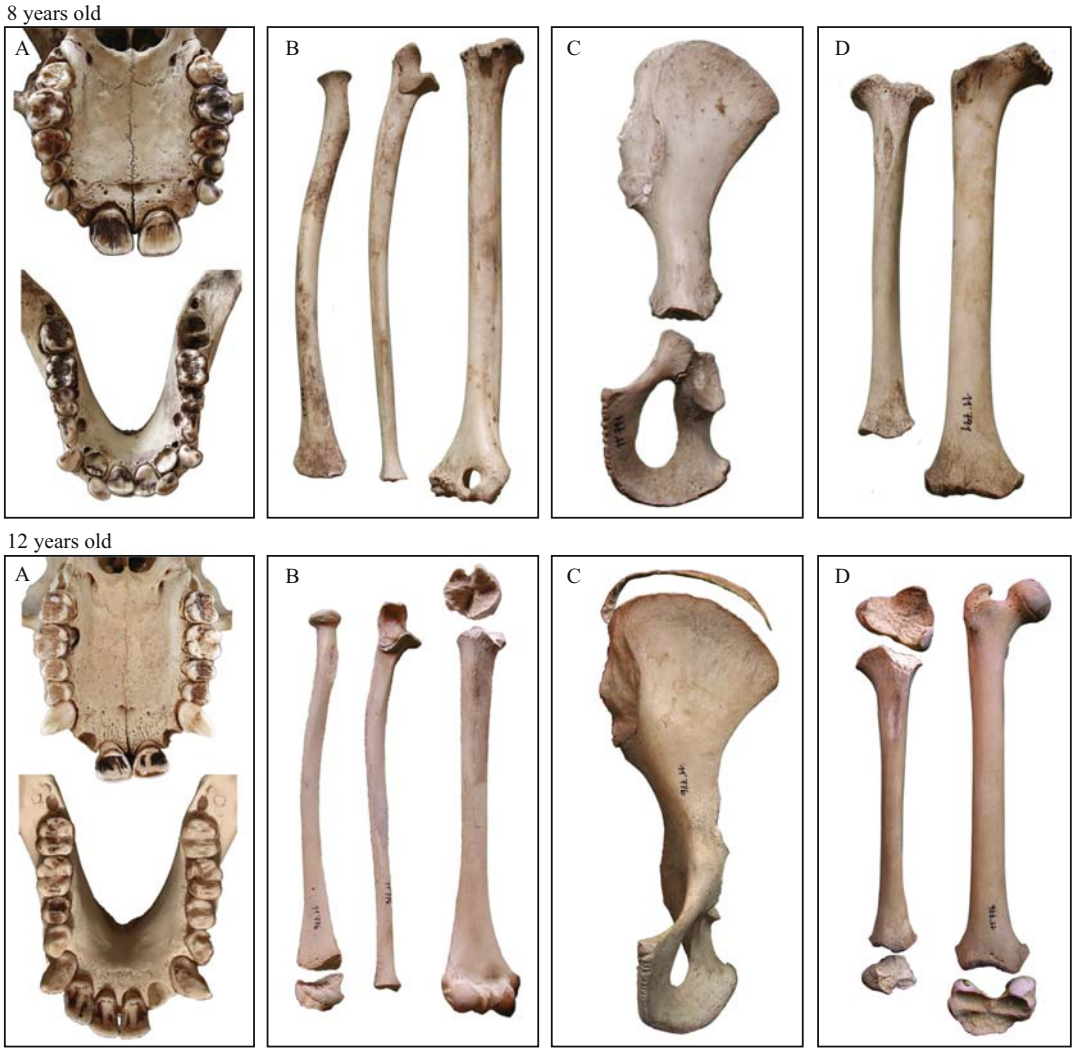
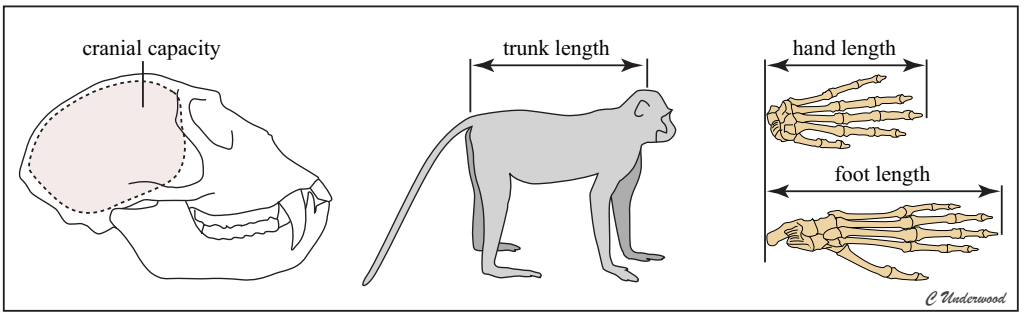


Fig. 15.5

Dentition and selected skeletal elements of *Top*: Immature 8-year-old wild chimpanzee. (A). Maxilla and mandible with deciduous second incisors, canines and molars; permanent first incisors, first and second molars; (B) Radius, ulna and humerus with all proximal and distal ends unfused; (C) Innominate unfused at the acetabulum (hip joint) and iliac crest; (D) Tibia and femur with all proximal and distal ends unfused. *Bottom*: Immature 12-year-old wild chimpanzee. (A) Maxilla and mandible with all permanent teeth erupted by third molars (second incisors lost postmortem); (B) Radius, ulna and humerus with elbow joint epiphyses fused (proximal radius, ulna; distal humerus) with distal radius, ulna and proximal humeral epiphyses unfused; (C) Innominate fused at the acetabulum (hip joint) but unfused iliac crest; (D) Tibia and femur with proximal elements of femur fused while all other elements unfused. After Bolter DR, Zihlman AL. Skeletal development in Pan paniscus with comparisons to Pan troglodytes. Am J Phys Anthropol. 2012;147:629–636.



Cranial Capacity (cc)	98
Tail, Foot, Hand (mm)	91
Femur, Trunk (mm)	86
Dentition	60
Body Mass (g)	59
Skeleton	56
Testes (g)	43
Muscles (mastication) (g)	41

Fig. 15.6

Mosaic timing of maturity across somatic features in immature and adult wild vervet population. *Modified from Bolter DR, Zihlman AL. Primate growth and development: a functional and evolutionary approach. In: Bearder S, Campbell C, Fuentes A, McKinnon K, ed.* Primates in Perspective. *Oxford: Oxford University Press; 2011:408–422.*

When cranial elements are preserved in the fossil record, brain growth can also be assessed relative to dental and skeletal maturation, as the vervet study shows. Body mass, a basic measure of body growth, records overall size increase, although no specific skeletal, dental or cranial measurement accurately correlates with or predicts it, so that body mass for a specific fossil is at best an estimate. In apes and humans, and in vervet monkeys as shown above, males grow for a longer period of time and reach dental eruption (canines), bone fusion (shoulder joint) and adult body mass later than do females. This female-male pattern of maturation leads to greater muscle masses in adult vervet males, a body composition pattern also found in both *Pan* and *H. sapiens*.[12,54,55]

The connection between dental stages and brain growth, that is, connecting eruption of the first permanent molars with completion of 90–95% of brain volume growth, has been correlated across catarrhine primates.[56] This research is particularly significant because (1) the pattern is conservative among a large taxon encompassing Old World monkeys, apes and humans (catarrhines); (2) two body systems are related, the neural and the dental; (3) dental emergence can serve as a marker for a stage of brain growth; and (4) teeth and jaws

are most often recovered in the fossil record and therefore these growth markers can be read in immature hominins.[57–59] Paleoanthropologists focus on the timing and pattern of tooth development, along with available postcranial remains in order to establish species patterns across somatic maturity events cf.[60]

Fossil evidence

Specific fossil sites

In primate and human research hard tissues like dentition, crania and mandibles, and postcranial skeletal parts thus provide the most useful comparative data for application to the study of immatures in the fossil record (primates: e.g., skeletal collections[17,45,47–49,62,63]; living primates: e.g.,[36,39,41–44,61]; humans: e.g., skeletal collections [64–65]; e.g., living humans [19,66–70]; cf. 10, 71). Interpretation of life stages and timing of developmental events of hominin ancestors is difficult for several reasons: (1) immature fossils are few and fragmentary; (2) limb and other bones of the postcranial skeleton are rarely preserved; and (3) how maturity interfaces with human-like features, such as large brain size and bipedal locomotion is not clearly understood.

Taung, South Africa. With Raymond Dart's discovery of the young Taung specimen, *Australopithecus africanus*, and his claim of its human ancestry, the study of immaturity made an appearance in paleoanthropology by default.[72] This single hominin specimen recovered from a lime-works cave comprised a complete face and maxilla, mandible with the first permanent molars, along with deciduous incisors, canines and molars (Figs. 15.2 and 15.7). In addition to the fossilized cranial bones, an associated and nearly complete endocast (fossil brain mold) was recovered which documented an ape-sized brain, at 382 cc, and at 406 cc estimated as an adult.[73] No postcranial bones were recovered at the site. However, the spinal column attachment at the base of the cranium, oriented underneath the head, suggested to Dart that Taung was a biped. Subsequent discoveries confirmed his supposition. Geological age of Taung is estimated between 2.6 and 3 million years old.[74]

The findings sparked controversy in the early studies of paleoanthropology, as many scientists of the time hypothesized that *H. sapiens* evolution was driven by selection for intelligence and a large brain, with bipedal walking occurring later in the course of evolution. To this end, Zuckerman[75] used an immature chimpanzee skull of comparable dental eruption as Taung in his analysis of Taung's cranio-facial dimensions. He argued that, as an adult, Taung's cranial and facial measurements would lie within the range of variation for chimpanzees, although the brain size would be slightly larger than that found in the African apes. This research reinforced a more ape-like affinity of australopiths rather than more human-like ancestry. The young juvenile Taung skull became incorporated into the human evolutionary tree after adult specimens of *A. africanus* were discovered and described.[76]

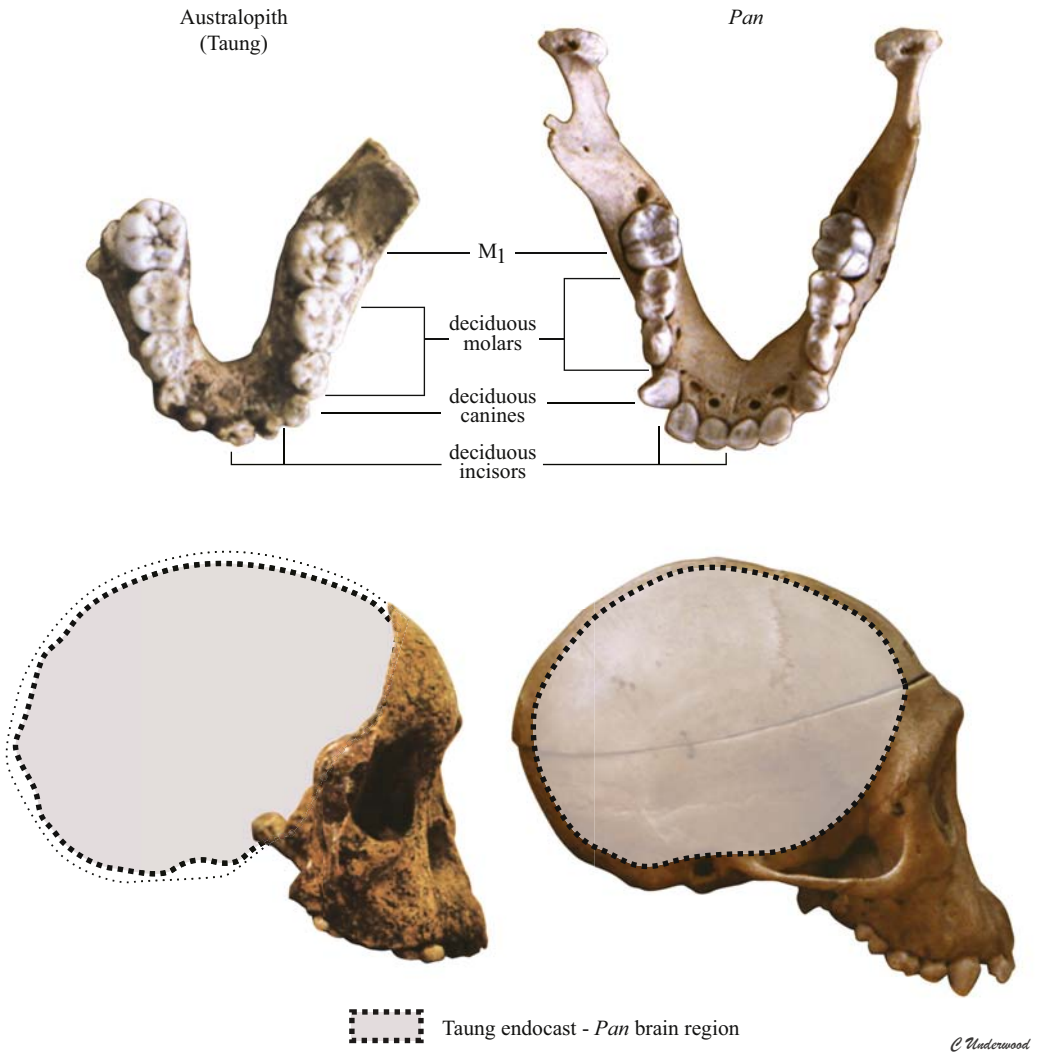


Fig. 15.7
Taung Child (*Australopithecus africanus*) and juvenile chimpanzee comparisons. Top: Mandibles. *Modified from Zihlman AL, Underwood CE.* Ape Anatomy and Evolution. *San Francisco: CreateSpace, Amazon; 2019.* Bottom: Crania and brain region.

Makapansgat, South Africa. In subsequent decades of fossil research, excavations expanded to other caves and additional immature specimens of australopiths were recovered. Cranial and postcranial elements were excavated from Makapansgat Limeworks in Plio-Pleistocene deposits estimated between 2.6 and 3 million years old.[74] An adult cranium (MLD 37/38) had an estimated cranial capacity of 435 mL.[77] An immature

mandible (MLD 2) had its first (M1) and second molars (M2) fully erupted and third molars (M3s) not yet erupted.[78,79] The dental complement included fully erupted but lost incisors, erupted first premolars (P3), and not yet erupted second premolars (P4); the right deciduous molar is preserved over the unerupted second premolar (P4). Dart noted that in humans, the premolars typically erupted before the second molars, and in humans, the second molars erupted ~ age 12 years. As the deciduous second molars were extremely worn, with the cusps nearly "obliterated", Dart concluded that these Makapansgat australopiths displayed a prolonged immaturity period comparable to modern humans, and aged the MLD 2 mandible using human standards at 12 years old.[78]

In the same gray breccia deposits as the MLD 2 mandible, two postcranial remains of an immature were recovered: the innominate bones of an unfused left ilium (MLD 7) and right ischium (MLD 8), which Dart hypothesized belonged to the same individual as MLD 2.[78,80,81] Subsequently, the same geologic horizon at Makapansgat yielded a second immature left ilium (MLD 25). This ilium duplicated elements of the first individual (MLD 7) in size, shape, and developmental stage, though was less robust which Dart attributed to sexual dimorphism. Consequently the MLD 25 individual was classified as a female and MLD 2, as a male.[79,82,83] Dart aged the two immature ilia at ~12 years based on the dental eruptions of MLD 2. He then compared the innominate materials to a 12–13 year old adolescent human pelvis of comparable maturational stage, that is, with completely unfused acetabulum.[80] The resulting australopith-human comparison showed consistency in size and proportions and confirmed for Dart that australopiths expressed a human-like growth pattern.[78,81] Dart's interpretation of a human-like pattern of maturity gave support to bipedalism as a more influential selective pressure in extending maturity, rather than brain size.

Kromdraai, South Africa. Immature hominin remains from the 1930s were recovered and classified by Robert Broom as a distinct species, *Paranthropus robustus*.[84–86] The type-specimen included a partial sub-adult cranium and mandible (TM1517a, b). The mandible included all permanent teeth, but with newly erupted and unworn M3. Subsequent work revealed immature postcranial remains of the right distal humerus and proximal ulna, along with an unsided distal hallical phalanx and a right talus, which were attributed to this same sub-adult.[84,85,87]; cf.[88] The geological age of these Kromdraai *Paranthropus* are uncertain, with an estimate of ~2.3–2 million years ago. cf.[88] Recent analysis of the type-specimen's dental development with skeletal fusion markers of the associated postcrania indicates *P. robustus* followed an ape-like pattern of maturity, not a human one.[89]

Olduvai Gorge, Tanzania. Fossil hominin discoveries in 1959 from Olduvai Bed 1 shifted attention to eastern Africa. A juvenile nearly complete mandible (OH7) was recovered from these geologic beds dated to 1.8 million years.[90] The permanent incisors, canines, premolars, first molars (M1s), and second molars (M2s) were fully erupted, though the

right side M2 was broken post-mortem; third molars (M3s) were not yet erupted. The mandible, associated parietal bones of the cranium, and hand bones served as the holotype for a new species named *Homo habilis*.[90] Although unusual to name a new species from an immature specimen, this individual had a distinctively larger cranial capacity than australopiths, originally estimated between 674 and 681 cc, cf.[79] with a recent estimate at 729−824 mL.[91] This large brain size, an undisturbed geological context, associated stone artifacts, and additional fossils (e.g. OH13) gave credence to the new taxon *H. habilis*, within modern human's genus, *Homo*.[90,92,93] Given the ape-like pace of maturity in early South African *Homo*,[94] an estimated an age-at-death of this specimen is ∼age 12 years.

West Lake Turkana, Kenya. The discovery of the nearly complete Nariokotome skeleton by Kamoya Kimeu, KMN-WT 15000 ("Nariokotome or Turkana Boy"), dated at 1.6 million years was assigned to *H. erectus*.[58,95] For the first time, a complete skull with immature dentition was associated *in situ* with unfused long bone elements and hip joint of the same individual. Dentally, most permanent teeth were erupted, except for the third molars (M3s), and the remaining deciduous upper canines. The acetabulum (hip joint) was without any fused elements.[96] This late juvenile skeleton more than the previous immature fossil hominin finds turned attention to the serious study of the evolution of human maturity and development. Originally the chronological age of this juvenile *H. erectus* was based on human standards − on human-paced dental eruptions, height estimates, and skeletal epiphyseal maturity. Consequently, the combination of these features gave an age at death estimate of 11−15 years.[58,64,69]

Methods to assess tempo of maturation in hominin fossils

With the discovery of immature fossil humans, chimpanzee tooth emergence served as an early method for timing maturational events in fossil species, such as with Taung. A new technique, CT scanning, exposed the state of enamel development. This technology made it possible to evaluate internal crown development of immature fossils with unerupted dentition.[97,98] With increased dento-skeletal samples from long-term field sites, wild chimpanzees provide a new comparative dataset on timing of dental eruptions and skeletal fusions.[10,17,45,47−49]

Microhistology. More detailed studies of dental development in fossils have focused on the histology of enamel formation of teeth.[99,100] Tooth crown formation builds upon a daily secretion of enamel that forms microscopic circadian lines on tooth surfaces. These daily "short" lines, combined with "long" lines laid down about every 9 days (range between 6 and 12 days[94]), called striae of Retzius, can be counted in tooth sections, or from their visibility on the tooth's surface, termed perikymata. Thus the chronological ages at death for a variety of immature fossil individuals can be directly established.[99,101−103] (Fig. 15.8).

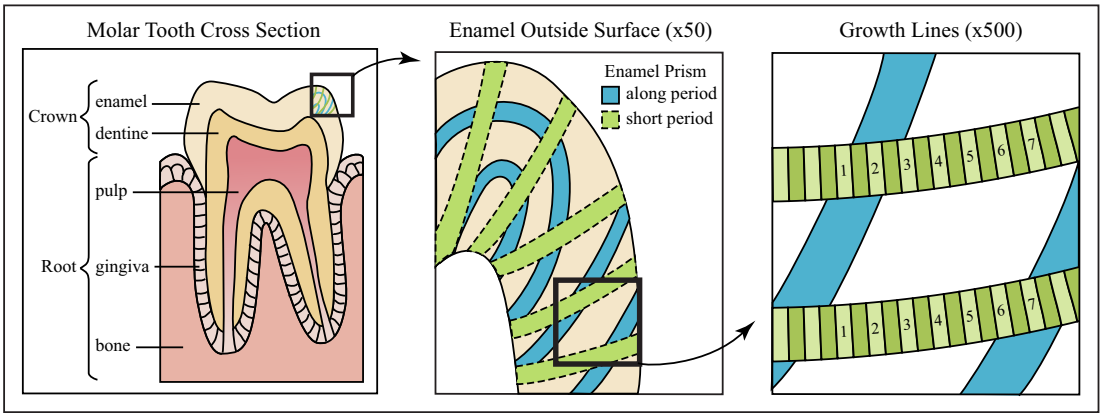


Fig. 15.8
Microhistology of daily and weekly incremental enamel secretions in dentition. *Modified from Zihlman AL.* The Human Evolution Coloring Book. *2nd ed. New York: HarperCollins; 2000.*

By the beginning of the 1990s application of this new technique confirmed in study after study quicker dental development in australopiths and early *Homo* compared to *H. sapiens.*[94,99–102,105] When applied to the perikymata of Nariokotome Boy, microhistology demonstrated an ape-like maturity pattern in *H. erectus* similar to the australopiths, and unlike *H. sapiens*.[103]

Current methods and case studies of immature hominin fossils

Dikika, Ethiopia. A skull and partial skeleton of an infant australopith (DIK-1-1) attributed to *Australopithecus afarensis* was recovered from Ethiopia in East Africa over the course of three excavation seasons from 2000–2003.[98,106] The fossil was dated to 3.3 million years.[98,106] Dentally, all the deciduous teeth are erupted, and all permanent teeth unerupted. The infant's brain size is estimated at 275 cc.[98,107] Using CT-scans and microhistology, the *A. afarensis* infant was aged 2 years 5 months at death,[107] consistent with an ape-like pace of maturity.[17] The find is particularly remarkable given that the skeletal elements are very fragile and typically such young individuals do not survive fossilization.

Malapa, South Africa. An immature juvenile male with partial skeleton, Malapa Hominid 1 (MH1), named *Australopithecus sediba* and dated to 1.98 million years may be one of the last surviving members of australopith populations thus far sampled.[108,109] This partially complete MH1 juvenile allows for a more thorough assessment of maturity patterns in the australopiths.[110] MH1 had second molars (M2s) fully erupted with long bone elements of the elbow (distal humerus and proximal ulna) fused. Unfused elements include a proximal femur, pelvis, and distal radius.[108,110] Both dentally and skeletally, the maturational pace is ape-like, and MH1 is estimated to be ~9–11 years old.[110] (Fig. 15.9)

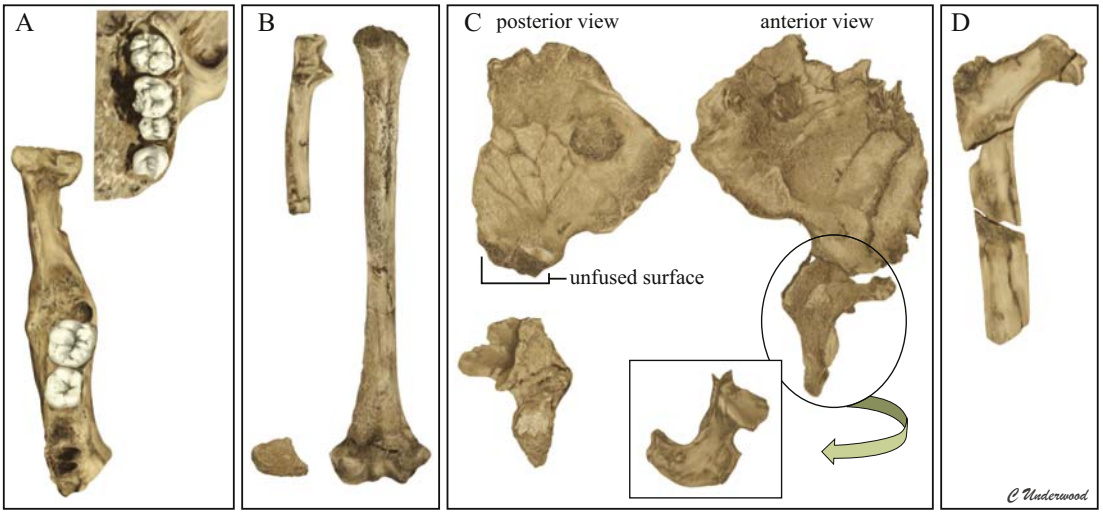


Fig. 15.9

Dentition and selected skeletal elements of Malapa Hominin 1 (MH1-*Australopithecus sediba*). Images taken from high quality cast. (A). Maxilla and mandible with permanent first and second molars; upper second premolar (P4) partially erupted; (B) Radius, ulna and humerus with elbow joint epiphyses fused (proximal ulna; distal humerus) with distal radius and proximal humeral epiphyses unfused; (C) Innominate unfused at the acetabulum (hip joint); (D) Partial femur with proximal elements of head and greater trochanter unfused. After Kibii et al.[111] and Cameron et al.[110]

West Lake Turkana, Kenya. The skeleton of KNM-WT 15000 offered the opportunity to focus on *H. erectus*, a species more closely related to *H. sapiens*. Some features like body size and proportions resembled modern humans, whereas its brain size at 880 cc was only twice that of the more ancient australopiths.[112] As noted earlier, based on human standards an age at death of 11–15 years was estimated for this specimen.[58,64,69] However, microhistologic analysis revised the chronological age-at-death for Nariokotome Boy to 7.6–8.8 years.[103,113] This surprisingly young age documented the persistence of a faster tempo of maturity for this member of the genus *Homo*. This finding casts doubt on the influence of either large body size or larger brain size as a selective agent to prolong maturity and extended life history stages over the course of human evolution.

Rising Star Cave System, South Africa. Discovery of a fossil bonanza, *H. naledi* from the Rising Star Cave site in South Africa, may shed light on the selective pressures shaping the evolution of human maturation.[114–116] The species sample has been discovered from the Dinaledi Chamber, dating between 335,000 and 226,000 years ago,[117] and the Lesedi Chamber, currently undated. The collection is distinctive in that individuals span all life stages: infants, young juveniles, old juveniles, sub-adult, young and old adults.[115,118,119]

Furthermore, the individuals recovered from Rising Star belong to one geographic population, and surprisingly, they appear to have purposefully disposed of their dead members.

A very recent age for the Rising Star's Dinaledi Chamber overlaps in time with at least three other *Homo* species − *heidelbergensis, neanderthalensis* and *sapiens.* Yet compared to its contemporaries *H. heidelbergensis* and *H. neanderthalensis, H. naledi* has an overall slighter build compared to modern humans, though height lies just within a modern *H. sapiens* range.[114,116,120] However, *H. naledi* brain size at 480−610 cc is less than half the size of modern humans.[114,117] Anatomically, *H. naledi* have modern-like hands and feet, bipedal pelvic, trunk and leg anatomy, and human-like dentition, whereas their torso and pelvis retain more primitive-australopith features.[114,116,121−126]

This fossil-rich Rising Star site provides paleoanthropologists with the opportunity to develop a demographic profile of life history features for a regional population of a recently extinct species, and across all life stages. cf.[127] The species can further test hypotheses regarding the influence of larger brain sizes, larger body sizes, dietary factors and behavioral competences as selective pressures that may have shaped maturational patterns during the course of human evolution.

Europe, Asia and the Near East. Neanderthals provide a relatively robust dataset for assessing maturity patterns in a fossil species. Multiple skeletal remains have been recovered, in part because the dead were intentionally buried, because they were recently extinct, and because caves were living sites. *H.neandertalensis* and modern *H. sapiens*, a closely related cousin, share genetic features that indicate common ancestry to ∼600,000 years ago and suggest interbreeding events between these two groups in Europe, Asia and the Near East.[128,129] Morphologically, Neanderthal brain sizes are large, as well as exceeding modern human ranges (1200−1600 mL). Body mass is estimated to lie within the modern human range. Although slightly shorter in stature, Neanderthal body proportions also lie within modern ranges cf. [130,131]

Immature individuals have been recovered from Western Europe, the Near and Middle East up through to 30,000 years ago, when they became extinct.[132−135]; cf. [131] Given the shared genetic relationships and morphological similarities, it is not surprising that dental molar microhistology and postcranial studies on maturity in Neanderthals fall within the range of human-like patterns.[132,134−136]; but see Ref. 137

El Sidrón, Spain. From El Sidrón, Spain a well-researched collection of Neanderthals consists of nine individuals recovered from the excavation, victims of a cannibalistic event with subsequent cave collapse, preserving the remains. The collection includes one nearly complete skeleton of a young juvenile with cranial, dental and postcranial elements.[135] The first permanent molars (M1s) are erupted, along with permanent incisors with the

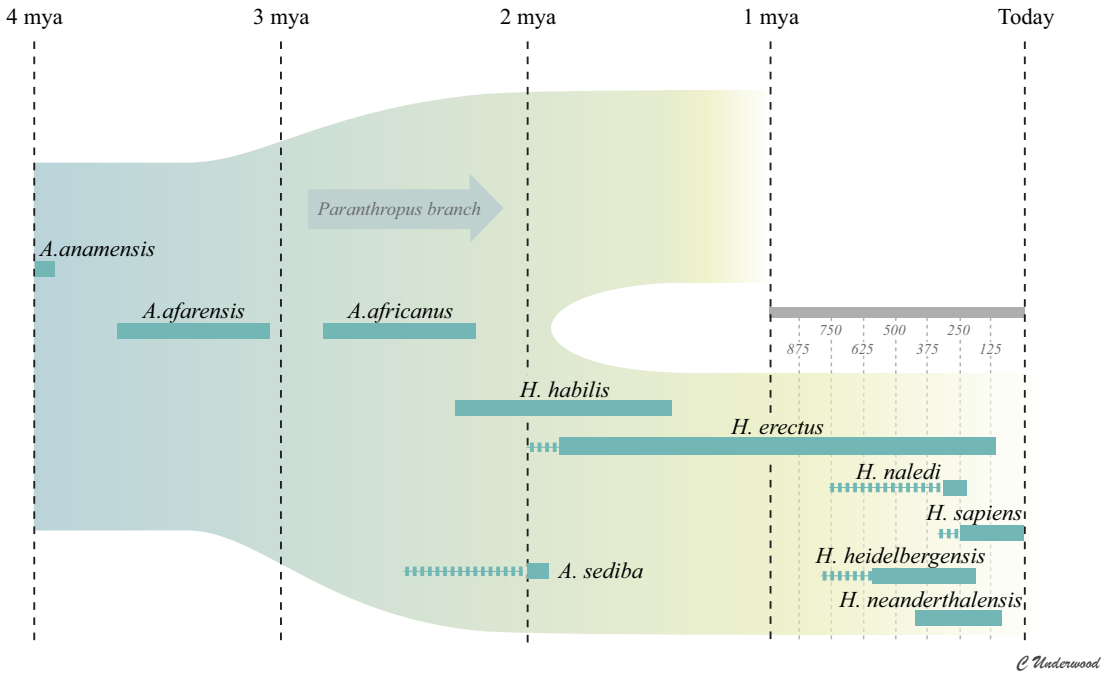


Fig. 15.10
Hominin phylogenetic tree, simplified, placing fossil species of *Australopithecus* and *Homo* discussed in text. Dashed lines represent estimated ages.

remaining dentition deciduous; most of the post-cranial skeleton retains unfused epiphyses. The dental microhistology gives the age for this individual at 7.7 years-at-death, and the dental and skeletal remains generally match those of a modern human of comparable age. Of interest are two elements that are less developed than a human juvenile of similar age: elements of the vertebrae and overall brain growth.[135] (Fig. 15.10).

Concluding thoughts

A number of issues regarding the evolution of the life history signature of modern humans remain unresolved among paleoanthropologists and anthropologists, for example, what is uniquely human in terms of maturation cadence, timing, development, and life stages, and how these features provide humans with an adaptive potential.[127,138–150] What seems convincing is that extension of life history stages during human evolution is a costly evolutionary trade-off. The individual must survive a longer immaturity before impacting the gene pool and consequently postponing reproductive age. For example, in modern human semi-foraging and foraging groups, pre-adult mortality is high (40.5%–65%) when compared to the range of pre-adult mortality across wild chimpanzee populations (27% –41%).[28–31,151] (Fig. 15.11). With increased sample sizes of immature fossil specimens

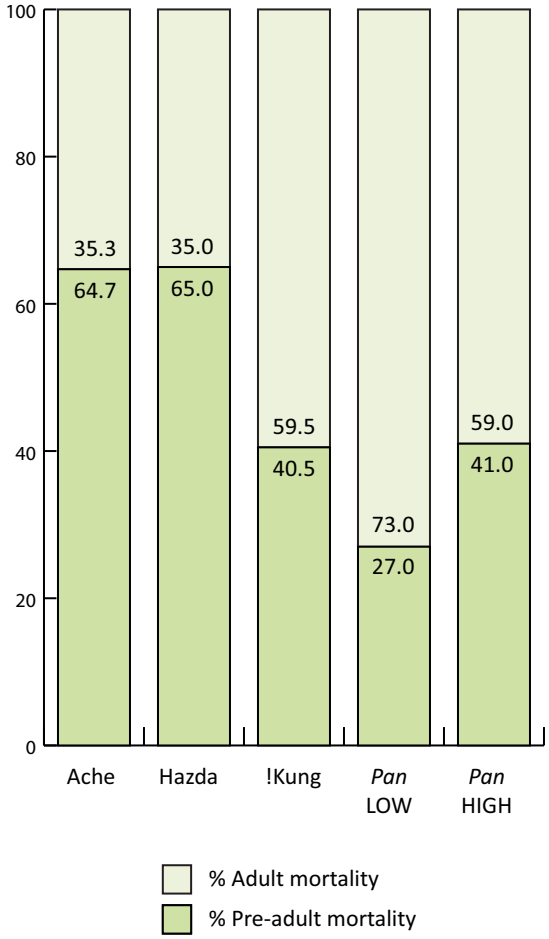


Fig. 15.11
Pre-adult mortality in foraging and semi-foraging modern humans compared to the averages and ranges across five wild chimpanzee populations.

and the discovery of new technologies to analyze these remains, paleoanthropologists continue to build a greater understanding of when, how and why humans take such a long time to mature compared to our ancestors.

Summary

Research methods and available datasets on growth and development in nonhuman primates provide a comparative model of dental, skeletal, cranial maturation to evaluate the sequence and rate of somatic maturity in *H. sapiens*. The genus *Pan* members, particularly wild chimpanzees, serve as the best living theoretical baseline for modeling

and assessing immaturity patterns during the course of human evolution. The hard parts of the body that fossilize allow study of past species' patterns — in dental eruption and its correlation with brain size growth, fusion of innominate and long bones, and body proportions. Taking into account the postnatal growth of the body as a whole across primate and human species, the species pattern of mosaic maturity is revealed in, for example, neural, dental, skeletal, body proportions, and these patterns shed light on forces of evolution shaping differences. The rich fossil record of ancient ancestors from the australopiths over 3 million years ago, through *H. erectus*, and Neanderthals, and new technologies for analyzing these remains, offer a basis for surmising about past lives, life stages, and life histories.

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CHAPTER 16

Early environments, developmental plasticity, and chronic degenerative disease

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Introduction

In recent generations, populations around the globe have experienced dramatic shifts in the burden of disease, with infections increasingly replaced by chronic degenerative diseases as the major causes of morbidity and mortality. Explaining these trends has been a central problem for demographers, epidemiologists, and biological anthropologists for some time.[1] A half century ago, Omran[2] proposed a demographic explanation for these trends in the concept of the "epidemiologic transition". He noted that when a population succeeds in controlling infant mortality related to early life infections and malnutrition, life expectancy increases, and as a result a greater percentage of the population survives long enough to be affected by chronic degenerative diseases that only emerge at older ages.

In addition to this role of population aging, modifiable lifestyle or environmental factors such as diet, physical activity, excess weight gain, smoking, or stress also influence the development of many chronic degenerative diseases. Although some of these factors may be viewed as lifestyle "choices", in many societies one's exposure to both favorable and harmful environmental and lifestyle influences can also be powerfully shaped by structural and systemic conditions that are often outside the control of the individual, including racism, class, and other forms of social oppression.[3,4] Taken together, the aging of the global population, combined with these lifestyle and social-structural dynamics, have traditionally been viewed as explaining the rising global burden of chronic diseases and their differential impacts among different groups within societies.

In this chapter, we will survey a literature that has helped bring a fresh perspective to our understanding of chronic disease epidemiology. Research in recent decades has shown that

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prenatal nutrition, stress, and other early life factors can influence risk for developing conditions like hypertension, diabetes, heart attack, and stroke in adulthood.[5] These relationships reflect the sensitivity of developmental biology to environmental experiences, which can have lingering effects that influence biology and health later in the lifecycle.[6] Furthermore, the unequal distribution of harmful exposures during early life, such as poor diet, traumatic stress, and various forms of socialized violence, may activate these developmental pathways to perpetuate and exacerbate existing social health disparities. Growing research suggests that an individual's risk of developing many adult chronic conditions may be established, in part, by such experiences much earlier in the lifecycle, often beginning prior to birth. By extension, some of the burden of disease in the current generation of adults may be traced to the social, environmental, and political conditions of their parents and other recent ancestors.[7,8]

In this chapter we will first review evidence from human populations that developmental responses to early life environments can influence adult risk for many common adult chronic degenerative conditions, with a primary focus on the cardiovascular diseases of hypertension, diabetes, heart attack and stroke. We will then briefly review some of the developmental and epigenetic mechanisms known to contribute to these relationships, before exploring the hypothesis that these sensitivities in developmental biology may have evolved to allow individuals to cope with changing environmental conditions. We conclude by considering the insights that this literature sheds on two central problems in public health: the rise of chronic disease in populations experiencing rapid nutritional or lifestyle transition, and the patterns of health disparities that map onto social gradients of inequalities related to class, ethnicity or socially-defined race.

Developmental origins of health and disease: evidence and mechanisms

Early environments, developmental biology and adult health

Beginning in the late 1980s, researchers in the United Kingdom observed that the risk of dying from cardiovascular disease (CVD), or of suffering from conditions that precede CVD like hypertension or diabetes, is highest among individuals who were light as newborns.[9–11] Now, hundreds of human studies have replicated similar findings relating lower birth weight to later CVD in populations across the globe, many using longitudinal designs that follow cohorts of individuals over decades as they age.[12–18] It is now well supported that individuals who were born small are more likely to have hypertension,[19] insulin resistance and diabetes,[20,21] abnormal cholesterol profiles,[22] a high risk visceral pattern of fat deposition,[23] and elevated risk of CVD mortality.[24,25]

Infancy and childhood nutrition and growth also predict adult biological and health outcomes. Not unlike birth size, small size in infancy is associated with higher CVD risk in adulthood,

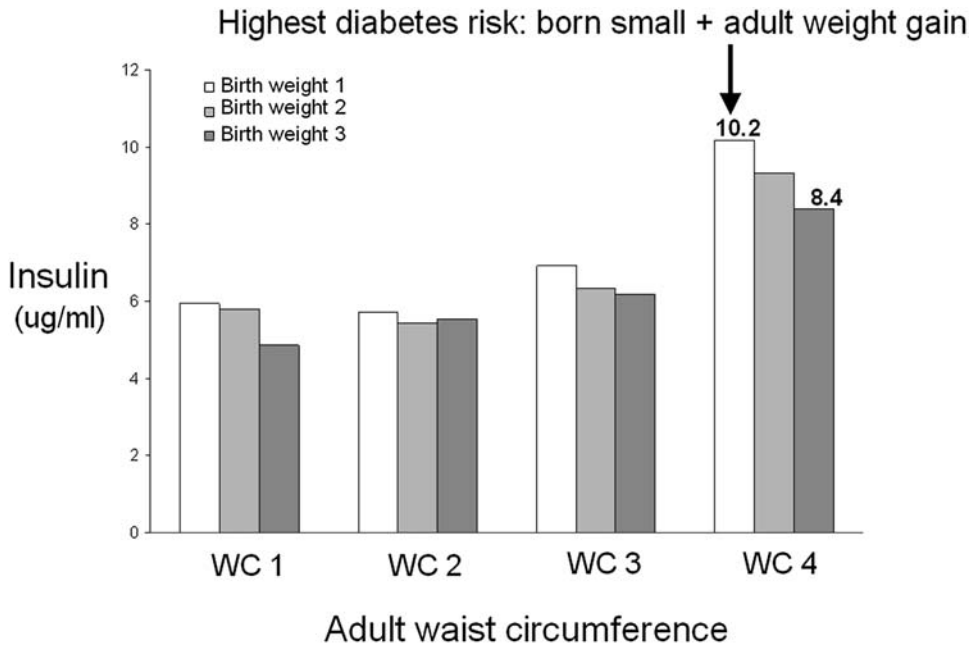

Fig. 16.1

How adult fasting insulin relates to birth weight and adult waist circumference among young men living in Cebu City, the Philippines (unpublished data). Men with more abdominal body fat as adults have higher fasting insulin, indicating higher risk of developing diabetes in the future. Note that the inverse relationship between birth weight and fasting insulin is strongest among the men who are heaviest as adults, and that the highest diabetes risk is found in men who were light at birth but then gained excess weight by adulthood.

while breastfed infants have lower rates of hypertension, obesity, and diabetes as adults.[26,27] There is also evidence that prenatal and postnatal exposures have interactive effects on adult health. For instance, being born small but gaining weight rapidly during childhood predicts the same cluster of adult chronic diseases.[28,29] Thus, it appears that the combination of small birth size and rapid weight gain during postnatal life may be an especially high risk scenario with respect to developing adult cardiovascular disease (Fig. 16.1).

Although much of this research has focused on nutritional stress, psychological stressors experienced by the mother during or even prior to pregnancy can lead to similar changes in disease risk in her adult offspring, and these effects can occur even in the absence of changes in birth weight. The fetus is normally shielded from exposure to the glucocorticoid hormone cortisol (a key stress hormone) produced by the mother's body by placental enzymes that inactivate the hormone. The placental capacity to buffer the fetus can be exceeded when the mother is severely stressed, leading to fetal exposure to maternal stress hormones. This in turn can contribute to reduced birth size by either

directly reducing fetal growth rate, or by leading to early pregnancy termination.[30] When the fetus is exposed to high levels of cortisol, this can lead to similar changes in CVD risk as observed after fetal nutrient restriction, including high blood pressure, changes in stress reactivity, a tendency to deposit fat abdominally, and resistance to the effects of insulin.[31] Collectively, this research is making clear that undernutrition or physiological stress experienced by the fetus prior to birth can influence risk of developing CVD and other chronic degenerative diseases in adulthood.

Mechanisms of developmental programming

What biological mechanisms might account for these relationships? Many of these studies relate adult health to birth weight, which is inherently challenging to interpret as a biological measure. Because birth weight partly reflects genetic factors, a relationship between birth weight and adult biology or disease risk could simply reflect the effects of any genes that influence both fetal growth rate and metabolic or physiologic processes that contribute to chronic disease risk in adulthood. For instance, insulin is not only related to glucose metabolism and risk of diabetes, but also helps regulate fetal growth rate. Thus, if individuals within a population vary in which insulin-influencing genes they carry, this could result in a correlation between fetal growth and adult risk of diabetes simply as a result of genetic correlations.[32,33] Although birth weight is a complex multifactorial phenotype,[34] there is now extensive evidence that the relationship between birth outcomes like birth weight and adult chronic disease are not simply due to genetic influences of this sort.

First, heritabilities for birth weight tend to be quite low. Based upon twin registries, heritabilities for birth weight are typically reported in the range 0.2–0.4 (e.g. [35–37]), with national birth weight registry studies finding similar estimates (0.31 for birth weight and 0.27 for birth length in all Norwegian births from 1967 to 2004;[38]). This implies that most of the variance in birth weight found within these populations traces to factors other than shared genetic ancestry. Other studies show that maternal influences like nutritional status, exposure to stress, or other factors influencing blood flow to the endometrial lining or placenta are important determinants of a baby's birth size.[39] Importantly, among monozygotic twins, who share identical genomes, the twin born lighter has elevated risk for adverse changes in body composition, risk for diabetes and hypertension later in life,[40,41] showing that differences in birth size predict adult CVD risk among genetically-identical siblings.

Perhaps the most important evidence that gestational experiences shape future adult health comes from animal model research, which has used experimentally-induced stressors to replicate many of the disease outcomes found in relation to lower birth weight in human populations.[42] For instance, restricting the nutritional intake of pregnant rats, mice, or sheep, or directly restricting blood flow to the fetus, increases postnatal blood pressure, cholesterol, abdominal fat deposition, and diabetes risk in offspring.[43,44]

Several types of biological adjustment are made by the developing fetus in response to prenatal stressors that contribute to these long-term changes in disease risk. All are examples of *developmental plasticity*, which may be defined as the capacity of the developing body to modify its structure and function in response to environmental or behavioral experiences. The most straightforward mechanism of plasticity involves changes in growth of a tissue or organ as reflected in size or cell number. For instance, the kidneys of prenatally-undernourished individuals tend to be smaller and have fewer nephrons, which increases risk of hypertension and renal failure in adulthood.[45,46] Similarly, changing the number or type of muscle cells can modify the body's ability to clear glucose from the blood stream, leading to changes in insulin sensitivity and diabetes risk.[47]

One increasingly well-studied set of mechanisms linking early environments with adult health involve *epigenetic* changes, which are defined as chemical modifications that change the pattern of gene expression in a specific tissue or organ without changing the nucleotide sequences of the DNA.[48,49] Several epigenetic mechanisms have received considerable attention for their likely role as links between early environments and adult health. For example, chemical modification of histone proteins that the DNA strands are wound around in the cell nucleus can lead to tighter or looser DNA packing in the region of specific genes, reducing or enhancing gene expression respectively. Methyl groups can also be attached in regions adjacent to specific gene promoters ("methylation"), which can impede binding by transcription factors and thereby silence gene expression in that cell.[50]

Experimental studies using animal models show that modifying nutritional or other characteristics of prenatal or early postnatal rearing environments can lead to durable epigenetic changes that persist into later life to influence biology and underlying processes that contribute to disease risk.[7,49,51] For instance (Fig. 16.3A), restricting the protein intake of pregnant rats reduces methylation of the promoter region of the gene that encodes an important stress hormone receptor (glucocorticoid receptor, GR) in the liver of adult offspring.[52] By reducing methylation—which reduces silencing of gene expression—this intervention *increases* expression of this receptor, enhancing the liver's metabolic response to stress.[53] In a similar rat model, maternal protein restriction was found to reduce methylation of the angiotensinogen receptor gene in the adrenal gland. The resulting *enhanced* capacity for expression of this gene could contribute to the high blood pressure observed in these animals.[54] In addition to these effects of maternal experiences on offspring health, there is now growing evidence that a *father's* experiences can influence epigenetic settings in sperm and be passed onto offspring, pointing to possible intergenerational health impacts of paternal experiences.[8]

The postnatal environment also has important influences on the epigenome. Well-described rat studies have shown that a nurturing maternal rearing style can lead to epigenetic changes in the brain of offspring (Fig. 16.3B), lowering their reactivity to stress and

reducing anxiety as adults.[55,56] In humans, untreated maternal depression or famine exposure during pregnancy have been shown to predict similar epigenetic changes in offspring, suggesting that comparable epigenetic processes may link early experiences with adult health in humans.[57,58]

In summary, we now have good confidence that the widely-documented relationships between early life measures like birth weight and later CVD partially reflect the effects of the gestational and infancy environments on the development of biological systems, including effects on how the body manages glucose and lipids, deposits fat, regulates blood pressure, and responds to stress (for further review see[59] Fig. 16.2). These effects typically reflect changes in the growth and development of specific organs and tissues or modifications in the regulation of hormones, metabolism or physiology. They are increasingly being traced to durable, environmentally-induced epigenetic changes in the

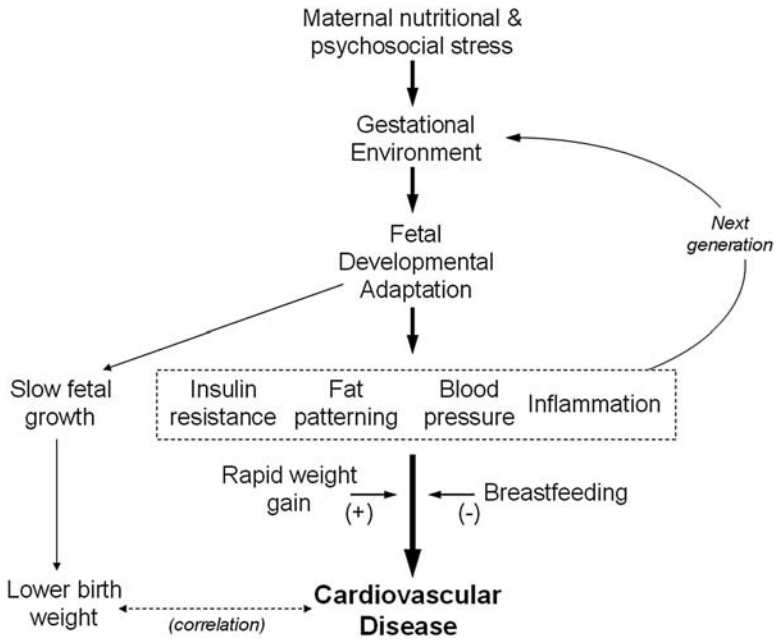

Fig. 16.2

The developmental origins of adult chronic disease. Maternal nutritional or psychosocial stressors influence the nutrient and hormonal characteristics of the gestational environment experienced by the developing fetus, which can durably modify multiple biological functions and elevate adult risk for cardiovascular disease (CVD). The arrow relating lower birth weight with CVD risk is dashed to indicate that the relationship is only correlational rather than causal. CVD risk is also elevated by rapid postnatal weight gain, and may be reduced by being breastfed. Some of the adverse adult biological effects of compromised early environments may in turn influence the maternal/gestational environment experienced by the next generation prior to birth, potentially perpetuating patterns of adverse health across generations.

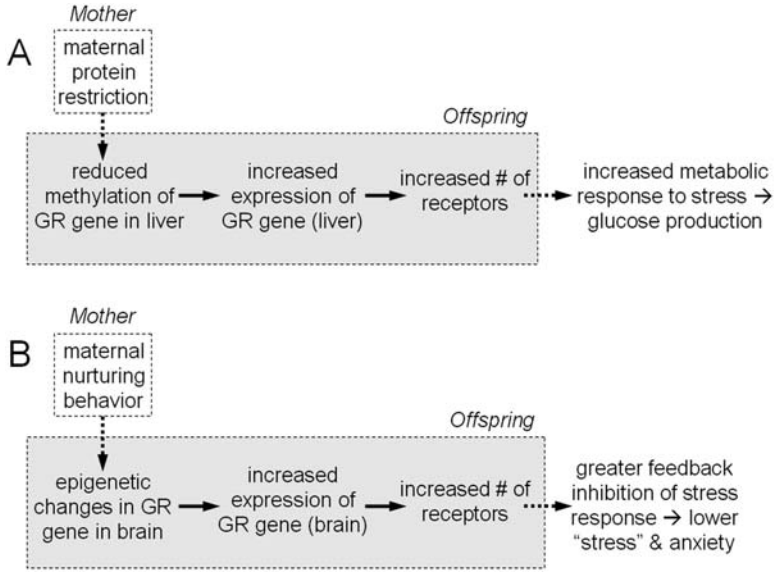

Fig. 16.3

Two examples of how early maternal experience or behavior can shape offspring biology via epigenetic changes in gene regulation: (A) when pregnant rats are fed a protein-restricted diet, this can reduce methylation of the receptor that binds to and senses stress hormones (glucocorticoids) in the liver of offspring. Because methylation generally suppresses gene expression, reducing methylation increases expression at the GR gene and thus increases the number of glucocorticoid receptors expressed in the liver. When glucocorticoids increase as a result of stress, these animals have an accentuated capacity to produce glucose for use as energy. This can help it cope with the stressor, but can also heighten risk of diabetes; (B) When rats are raised by nurturing females, they exhibit complex epigenetic changes that increase expression of glucocorticoid receptors, this time in hippocampal (brain) neurons. When these animals experience stress later in life, the increased number of receptors allows the brain to quickly sense rising hormone levels and shut down further stress hormone production. This contributes to a blunted stress response that reduces anxiety. *Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring.* J Nutr. *2005;135(6):1382–1386; Weaver IC, Cervoni N, Champagne FA, et al. Epigenetic programming by maternal behavior.* Nat Neurosci. *2004;7(8):847–854.*

chromosomes that modify gene expression in specific tissues or organs without modifying the DNA itself.

Developmental plasticity as a means of adaptation

Early life developmental plasticity and adaptation to ecological change

Why might the body modify its developmental biology in response to early life stressors? Some of the lingering effects of early experience on adult health simply reflect unintended

side-effects of adaptations made by the fetus to improve its chances of surviving a nutritionally stressful prenatal environment. For instance, a smaller fetus has lower nutritional needs, and the reduced ability of their smaller muscle mass to clear glucose from the blood stream could spare energy for the glucose-hungry brain, which is fragile and large relative to the body during early life.[60,61] Another possibility, which in some ways may be the most straight-forward, is incomplete buffering of the fetus against maternal stressors.[62] A failure of the mother's body, or the placenta, to fully buffer the developing body from early stressors can lead to impairments with long-term unintended side effects on biological function and health.

Although these non-functional explanations for plasticity clearly are important, it has also been speculated that developmental plasticity could, in some instances, allow the fetus to prepare for conditions likely to be experienced *after* birth[63–66](Fig. 16.4). Some of the adjustments made by the nutritionally deprived fetus *in utero*, such as a tendency to deposit more abdominal body fat, and the reduced response of muscle to insulin that spares glucose for use elsewhere in the body, could provide advantages after birth if the postnatal environment is also nutritionally deprived.[65,67] In addition, other systems that change settings in response to early environments, such as stress physiology,[55] immunity,[68] and reproductive biology[69] might also be "fine-tuned" in response to early experience.

One challenge to this idea comes from the fact that humans have a long lifespan. Because we typically live many decades, any conditions that we experience during a few months of early development, such as gestation or early infancy, may not be reliable cues of environments likely to be experienced decades in the future.[64,70] One intriguing possibility is that it is precisely the brief and early timing of many of the body's periods of

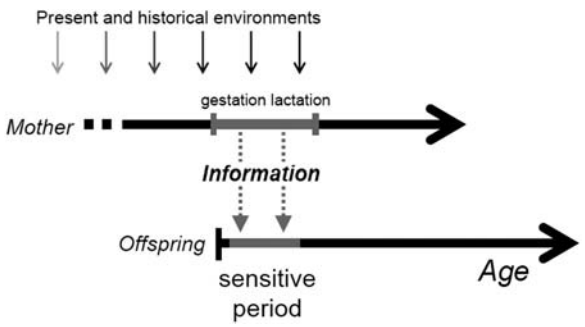

Fig. 16.4

Maternal-offspring ecological information transfer and adaptation. The mother's biology and behavior embody a record of her cumulative environmental and social experiences, which can be conveyed to offspring as developmental information via nutrients, hormones, rearing behavior and other cues. *From Kuzawa C, Quinn E. Developmental origins of adult function and health: evolutionary hypotheses.* Annu Rev Anthropol. *2009;38:131–147, with permission.*

heightened developmental sensitivity that paradoxically *helps* the developing organism overcome the challenge of reliably predicting conditions well into the future.[62,71] Here the idea is that the mother's physiology could buffer the fetus against the day-to-day, month-to-month or seasonal fluctuations in the environment, while passing along information about local conditions that is more stable and reliable. Because the mother's biology and behavior have been modified by her lifetime of experiences, the nutrients, hormones, and other resources that she transfers to the fetus *in utero*, or to her infant via breast milk, could correlate with her average experiences more than what she is experiencing during any week or month of gestation itself.[64,70]

Perhaps the best evidence for such a capacity to convey average, rather than transient, ecological information comes from studies of the effects of a mother's nutrition on the birth weight of her baby.[64] Studies generally find that birth weights tend to be lighter in populations in which nutrition has been marginal for multiple generations. Despite this evidence for environmental influence on fetal growth rate and birth size, supplementing pregnant women often has minimal effects on the birth weight of her offspring.[72,73] Thus, it appears that long-term history in an environment may be an important influence on the resources transferred in support of offspring growth, but that fluctuations in intake during pregnancy itself—reflected for instance in dietary supplementation—have comparably modest effects.

This *phenotypic inertia* – reflecting the lingering biological but non-genetic effects of the mother's average experiences in the past – could allow the fetus to track those dynamic features of environments that are relatively stable on the timescale of decades or several generations (see [64,74]). This could allow adjustment to environmental changes that are too rapid to result in modifications in gene frequencies via natural selection, which requires many generations, but that are too chronic to be buffered efficiently by reversible homeostatic processes. In this way, the mother's body could pass along biological "memories", reflecting her own lifetime of experiences in the local environment, along to her developing offspring, allowing developmental adjustments to be made in anticipation of conditions likely to be experienced locally.

Implications of developmental programming for social health disparities

So far we have surveyed some of the evidence that early life stressors can have health effects that linger into adulthood and in some instances may even transcend the present generation to be passed on to offspring. These findings hold promise to help explain why patterns of health and disease tend to relate strongly to differences in environmental, social, and economic experiences both within and between populations. There is growing evidence that early environment-triggered developmental plasticity can help clarify two broad problems in the social distribution of public health burdens: disease transitions in

populations experiencing rapid cultural, nutritional or lifestyle change, and health disparities within populations marked by chronic inequality and social stratification related to class, gender, and race. We end our discussion by briefly reviewing the case that developmental processes contribute to each of these public health issues.

High risk scenario 1: when early life undernutrition is followed by adult weight gain

Above, we discussed the hypothesis that the fetus has a capacity to "anchor" its nutritional expectations to a gestational signal (e.g. hormones, nutrients) of average recent nutrition as experienced by the mother. This might allow the developing organism to modify its own nutritional expenditure, as reflected in its growth rate, body size and other traits, as locally experienced nutritional conditions change. It is easy to see how metabolic changes that could be favorable to a nutritionally-stressed fetus or infant—such as sparing glucose, or depositing more fat in the abdomen—might also plant the seeds for heightened risk of developing metabolic diseases if that individual ends up gaining weight rapidly during childhood or as an adult. Thus, any context in which individuals routinely face nutritional stress prior to birth or during infancy but then gain excess weight during later childhood or as an adult should be associated with high susceptibility of developing metabolic disease.

The now common finding that CVD risk is highest among individuals who were born small but later put on weight is consistent with this idea.[23,75] Under what societal conditions might this pattern of early dearth followed by later excess be especially prominent or influential within a population? One way is as a result of rapid cultural, political or economic transition.[76] In many societies, industrialized farming has increased the affordability of cheap calories,[77] while populations are also relying more and more on automobiles and other forms of transportation to move from place to place.[78] As individuals take in more calories while expending fewer during the day, weight gain is inevitable. When the transition to relative caloric excess takes place within a single generation, individuals raised under austere nutritional conditions during early life may go on to gain excess weight as older children or adults and have heightened CVD risk as a result. Consistent with this model, stunting—a measure of early life undernutrition—has been shown to be a risk factor for metabolic syndrome and obesity in populations experiencing rapid nutritional transition.[79–81]

Take the South African case as an example. South Africa notoriously faced a dramatic double burden of infectious disease epidemics due to rapid rise in HIV/AIDS and tuberculosis rates in the mid-1990s to mid-2000s, leading to a dramatic increase in overall mortality during this time period. Fortunately, political organizing and medical innovation helped curb the diseases' morbidity and mortality rates. Yet the new democracy also experienced rapid modernization and socioeconomic development – largely driven by the exploitative capitalist policies of apartheid that created high demand for dispensable,

low-wage labor, displaced communities from rural settings to racially segregated, urban informal settlements, and limited opportunity for social mobility and political power among non-White communities.[82] These large societal transitions resulted in the adoption of higher fat and protein diets, physical inactivity, and other "obesogenic" and industrialized environments that pose a variety of risk factors for cardiovascular, metabolic, and other non-communicable diseases.[83–86] Recent research from longitudinal studies of children born near the end of apartheid shows that poor early growth profiles, characterized by low birth weight and greater relative weight gain in infancy, predicts greater risk for high blood pressure and hypertension in adolescence and adulthood.[87,88]

Poor early life nutrition may also coexist with adult overnutrition simply due to the fact that nutritional stressors are often concentrated during periods of heightened nutritional vulnerability early in the lifecycle. In contrast to trends toward positive adult energy balance and weight gain in many global populations, the nutritional experiences of infants and young children are often more strongly influenced by common communicable diseases and their underlying social determinants, such as sanitation, crowding, and availability of clean water. That nutritional stress around the age of weaning is often severe is revealed by the mammalian strategy of depositing extra body fat after birth in preparation for weaning. Even among mammals, humans give birth to the fattest babies on record, which may help us prepare for this weaning stress, which is accentuated in our species owing to the need to provide a constant supply of energy for our unusually large and energetically fragile brains.[89,90]

It is an unfortunate fact that in many developing economies today, nutritional stressors at this early age tend to be common—tracing to factors like diarrhea and respiratory tract infections—despite the fact that those same individuals may later experience excess weight gain as adults. Because infancy nutrition remains tightly linked to social conditions related to poverty, while availability of cheap calories is increasingly common and driving adult weight gain, many individuals may now experience early life nutrition stress followed by adult caloric excess even in the absence of rapid societal transition. This is reflected for instance in the common co-occurrence of obese and malnourished individuals in the same household within some low income populations.[91] The body's developmental response to early nutritional stressors can help explain why these populations often have high rates of cardiovascular and other metabolic diseases.[76]

High risk scenario 2: the social origins of health disparities related to race, class, and gender

In addition to helping explain heightened CVD risk in scenarios of early life undernutrition followed by later nutritional excess, the developmental origins framework can also help explain why CVD and related metabolic diseases tend to map onto social

categories such as class, gender, ethnicity, and race. These social health disparities are among the most pressing of contemporary public health issues.[4,92,93]

As one well-studied example, in the United States, African Americans on average have a higher burden of many cardiovascular diseases, including hypertension and diabetes, compared to other demographic subgroups.[94,95] When studies find that self-identified race is still a significant predictor of these conditions after statistically adjusting for various lifestyle and socioeconomic characteristics, some researchers have been tempted to conclude that genetic factors might explain the black-white difference in health. The problem is that there is in fact very little evidence for a genetic contribution to these health differences,[96,97] which instead relate powerfully to the social and environmental conditions in which these health disparities manifest.

Importantly, these factors often reflect influences beyond the control of individuals, such as unequal patterns of police violence, healthcare access, and economic opportunity.[98–101] For instance, chronic stressors like everyday racism, housing discrimination, neighborhood segregation, and anti-black racism can worsen health and life outcomes through a number of pathways, such as increased psychosocial stress, limited access to healthy food options, and greater risk for mass incarceration.[102–104] These exposures to chronic stress may become physiologically "embodied" through persistent activation of stress-sensitive pathways, such as the neuroendocrine and immune system, which in turn may lead to greater damage to the human vasculature through atherosclerotic build-up in the arteries, higher blood pressure, and greater concentrations of glucose and fatty acids in the bloodstream.[105]

These effects of unhealthy environments on adult health are not surprising, and in fact are well established. Where these traditional effects of stressful environments converge with our present story is in the realization that they *also* contribute to poor birth outcomes and compromised gestational environments, which can have health effects that linger into adulthood, and even transcend the present generation of adults.[106] Indeed, African Americans not only have higher rates of adult CVD, but are also disproportionately affected by the early life antecedents to these conditions, such as a lower mean birth weight, intrauterine growth retardation and premature delivery, which are also known consequences of structural racism.[107,108] Similarly, these early life health disparities are not strongly related to genes, but instead are linked to factors like stress and discrimination, limited access to healthcare, and constraints on social mobility.[109,110]

Bringing these threads of evidence together suggests that the developmental and intergenerational processes discussed above are likely an important part of the story of US health disparities.[106] Imagine the following sequence of effects. First, a pregnant mother experiences chronic stress that elevates her production of stress hormones (e.g. cortisol) during pregnancy. As the level of this hormone rises, the ability of the placenta to shield

the fetus from it is exceeded, and the fetus is exposed to high levels of this maternal hormone. This modifies various aspects of developmental biology, for instance by changing how the offspring's body regulates stress hormones, glucose homeostasis, blood pressure or fat deposition.[111] Some of these changes involve epigenetic or developmental modifications in the regulation of organs, tissues, or metabolism, which are relatively durable. Later in life, the offspring—now an adult—is more likely to have high glucose, insulin, blood pressure or stress hormones as a result of these early life effects. In this way, stressors experienced unequally by the adults of one generation—the mother during pregnancy—might contribute to adult health disparities in the next generation of offspring. Importantly, these embodied experiences of stress, trauma, and discrimination are likely to be worse among individuals and communities who face compounding and intersecting forms of societal oppression, such as in instances of racial trauma, gender-based violence, and xenophobia.[112,113]

The story unfortunately does not stop here, however, because among these adult offspring are females who become pregnant and have children of their own. How might the original stress experienced by the mother effect the health of her grandoffspring? The simple answer is that we do not know because studies have yet to investigate this definitively in human populations, and the reversibility of such effects has similarly been understudied. But there are reasons to suspect that the original stressor could have some lingering effect that is passed on, albeit weakly, across several generations. This is because some of the long-term effects of an adverse gestational environment on adult health in offspring, such as insulin resistance, high blood pressure, or inflammation, can negatively impact the gestational environments experienced by the next generation, and can also lead to lower birth weight deliveries (Fig. 16.5). In this way, lifecourse influences of early life stressors can be transformed into intergenerational pathways for the perpetuation of health disparities across generations.[114] This type of intergenerational transmission is believed to help explain why conditions like gestational diabetes can influence health in multiple generations of offspring, potentially amplifying obesity or diabetes rates across generations.[106]

Conclusion

In this chapter we have seen how fetal and infancy stressors can influence developmental biology to modify one's risk of developing many common degenerative diseases as one ages, including but not limited to hypertension, diabetes, heart attacks, and stroke. This research shows how adult health in one generation may be linked with the environmental experiences of recent ancestors, especially the mother during and prior to pregnancy. We have also surveyed biological mechanisms underlying these effects, and considered the insights that these findings bring to our understanding of two common contexts for

Fig. 16.5

A life course, intergenerational model of health disparities. Maternal stressors influence biological settings and health of her offspring. In female offspring, some of these changes persist into adulthood to influence the gestational environment experienced by the grandoffspring. Thus, developmental responses to early environments can perpetuate patterns of health disparity not only across lifecycles but potentially also across generations. *Modified after Kuzawa C. The developmental origins of adult health: intergenerational inertia in adaptation and disease. In: Trevathan W, Smith E, McKenna J, eds.* Evolutionary Medicine and Health: New Perspectives. *New York: Oxford University Press; 2008:325–349.*

socially-driven disease in contemporary human populations. The first involves situations in which an individual experiences nutritional or infectious disease stressors early in life but subsequently gains weight rapidly during childhood or adulthood owing to caloric excess and positive energy balance. The second example is the tendency for health inequality to map onto social gradients of privilege, opportunity, discrimination and stress within societies, as exemplified by the stark differences in health that typically relate to class, ethnicity and socially-defined race. The developmental origins framework shows one set of mechanisms by which social inequalities can become embodied physically as health inequalities in the next generation, operating through effects of maternal biology on offspring development. Collectively, these findings point to the long-term benefits to society of ensuring adequate nutrition, health care and buffering of stress among pregnant women and their young offspring.

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Suggested readings

Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *Br Med J*. 1989;298(6673):564−567.
A classic early study demonstrating a link between size at birth and adult cardiovascular disease mortality.
Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359(1):61−73.

Reviews evidence for developmental influences on adult health and disease.

Kuzawa C, Quinn E. Developmental origins of adult function and health: evolutionary hypotheses. *Annu Rev Anthropol*. 2009;38:131−147.

Reviews evidence that early developmental plasticity allows organisms to adapt to the environment.

Victora CG, Adair L, Fall C, et al. Maternal and child undernutrition: consequences for adult health and human capital. *Lancet*. 2008;371:340−357.

Reviews evidence for long-term effects of early environments on adult health in five developing country cohort studies.

Drake A, Walker B. The intergenerational effects of fetal programming: non-genomic mechanisms for the inheritance of low birth weight and cardiovascular risk. *J Endocrinol*. 2004;180(1):1−16.

Presents a model for the intergenerational perpetuation of the adverse effects of maternal stress across multiple generations.

Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. *Annu Rev Nutr*. 2007;27:363−388.

Reviews evidence for epigenetic contributions to the developmental origins of adult disease.

Internet Resources

Official Webpage of the International Society for Developmental Origins of Health and Disease http://www.mrc.soton.ac.uk/dohad/.

CHAPTER 17

Physical activity and growth

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It is now established beyond any doubt that physical activity is essential for the health of children and adolescents. This includes healthier body composition,[1] improved cardiometabolic,[2] musculoskeletal,[3] cognitive,[4] and mental health outcomes.[5] Physical activity has shown moderate tracking from childhood through, adolescence[6] and adolescence into young adulthood[7] and, thus, many believe that enhancing physical activity during childhood and adolescence could translate into lifelong health gains.

Despite the known benefits of being active, the majority of children and adolescents globally do not achieve the minimum recommended levels of physical activity for health benefits.[8] Organized sport is the most popular and visible form of structured physical activity in youth. In the United Kingdom it is estimated that approximately 37% of children participate in organized sports outside of school.[9] While attendance in organized sport has increased in some countries over the last two decades,[10] particularly at the younger ages, children's participation in sport is on the decline, especially among youth of low socioeconomic position.[11] Thus, increasing physical activity among children and adolescents is a major public health goal in most countries.

As outlined in this book, in humans the onset of puberty can vary by as much as seven to eight years, with girls typically entering puberty a year in advance of their male counterparts, as indicated by changes in the production of Gonadotropin Releasing Hormone. Variance in the timing and rate of growth and maturation has been shown to have important implications for both physical and psychosocial development[12] and these consequences are especially salient in the context of physical activity. However, while many studies in public health consider growth parameters as a descriptor (e.g. stature, and weight) and as a correlate or outcome (e.g. body mass index), and biological maturity (e.g. stage of sexual development) as a confounding influence/covariate in analyses, there has been little studies directly examining the impact of growth and biological maturity on physical activity behaviors, or vice versa. However, within the field of Sport and Exercise Science, there has been ample observational research documenting growth and development as an important predictor of performance and selection in young athletes.

Human Growth and Development. https://doi.org/10.1016/B978-0-12-822652-0.00006-7

This chapter will provide a brief overview of physical activity more generally, including an outline of measurement issues and methodologies, physical activity guidelines, health outcomes and correlates. For an in-depth overview of these topics, which are beyond the scope of this chapter, we point readers to a recent book on Youth Physical Activity.[13] We will then provide a more critical overview of some of the topical research and practice debate that are specific to physical activity and the human growth and development of children.

Definitions of physical activity/sedentary behavior

Physical activity is a complex behavior and perhaps even more so in children and young people, and, by definition, includes "any bodily movement produced by the skeletal muscles that results in a substantial increase in energy expenditure above resting".[14] In children and adolescents this could include, but not limited to, active (e.g. walking, scootering, biking) travel, active play, sports and exercise (for example, the recently popular active mile programmes offered in schools). Related to inactivity (but not to be used synonymously) is sedentary behavior, "any waking behavior (such as school work, watching TV or being driven to school) characterized by an energy expenditure $\leq$1.5 metabolic equivalents (i.e. METs) while in a sitting or reclining posture".[15] Historically, the term sedentary was used often to describe children that were not meeting physical activity guidelines (such as at least 60 min of moderate-to-vigorous physical activity (MVPA) per day). However, it is now widely recognized that MVPA and sedentary behavior are distinct behaviors (i.e. they can co-exist); in that a child could accrue many hours of sitting throughout the day and but can still meet physical activity guidelines (e.g. via after school sports clubs). High levels of sedentary behavior are an independent predictor of poor physical[16] and mental[17] health in children and adolescents.

Physical activity and health and wellbeing

The evidence to date surrounding physical activity and health outcomes is generally robust, with most associations supported by systematic reviews (e.g. [18,19]) of high quality (e.g. including only device assessed physical activity) research. This section reflects what we know from a summary of systematic reviews[20] published alongside the most recent WHO physical activity guidelines for children and young people (5–17 years). There is a large evidence base to support the associations between greater volumes and higher intensities (such as moderate-to-vigorous intensity) physical activity with multiple beneficial physical health outcomes in children and adolescents, including cardio-respiratory fitness, muscular fitness, body composition, cardiometabolic health, and bone health. Physical activity can also reduce the risk of experiencing clinical and non-clinical depression (which accounts for 16% of the global burden of disease and injury in people aged 10–19 years[21]) and enhance cognitive function (e.g. executive function) and academic outcomes in children and adolescents. While, intuitively it would seem sensible

that enhanced physical activity would be associated with more proficient motor development and sleep, the evidence is currently inconclusive. Importantly, there is no evidence to support adverse events (e.g. injuries) associated with greater participation in physical activity. Some benefits are specific to the type of physical activity for example, active transport has been associated with greater vitamin D. Relevant to this chapter, sport hosts an array of specific benefits outside of physical health including social (e.g. sportsmanship), psychological (e.g. increased self-esteem, particularly with team sports[22]), positive leadership[23] and superior neurocognitive functioning.[24]

Greater time spent sedentary, in particular recreational screen time, is associated with poorer health outcomes in children and young people, including poorer fitness, cardiometabolic health and unfavourable body composition. With regards to mental health the evidence varies by type of sedentary behavior with excessive TV viewing and video gaming being associated with lower pro-social behavior and reading and homework associated with higher academic achievement.

Physical activity guidelines

Historically, we have seen a variety of physical activity recommendations globally that have evolved as the evidence base grew. The last two years has seen the updating of several national physical activity guidelines and most recently the Global physical activity guidelines by the WHO. While, there may be slight differences in individual national guidelines the majority have centered around a set of core recommendations that align quite closely with the WHO Guidelines that were published in 2019 for 1−5 year olds[25] and in 2020 for 5−17 year olds.[26] The guidelines for children under 5 years differ from the children and adolescent guidelines in that they consider the full 24 h (i.e. including sleep) and have more detailed (prescriptive) guidance surrounding sedentary behavior.

Infants (<1 year) should:

- Be physically active several times a day in a variety of ways, particularly through interactive floor-based play; more is better. For those not yet mobile, this includes at least 30 min in prone position (tummy time) spread throughout the day while awake
- Not be restrained for more than 1 h at a time (e.g. prams/strollers, high chairs, or strapped on a caregiver's back)
- Screen time is not recommended
- Have 14−17 h (0−3 months of age) or 12−16 h (4−11 months of age) of good quality sleep, including naps.

Children (1−2 years) should:

- Spend at least 180 min in a variety of types of physical activities at any intensity, including moderate-to-vigorous-intensity physical activity, spread throughout the day; more is better.

- Not be restrained for more than 1 h at a time or sit for extended periods of time. For 1-year-olds, sedentary screen time (such as watching TV or videos, playing computer games) is not recommended. For those aged 2 years, sedentary screen time should be no more than 1 h; less is better. When sedentary, engaging in reading and storytelling with a caregiver is encouraged.
- Have 11–14 h of good quality sleep, including naps, with regular sleep and wake-up times.

Children (3–4 years) should:

- Spend at least 180 min in a variety of types of physical activities at any intensity, of which 60 min is moderate-to- vigorous-intensity physical activity, spread throughout the day; more is better.
- Not be restrained for more than 1 h at a time or sit for extended periods of time.
- Sedentary screen time should be no more than 1 h; less is better.
- Have 10–13 h of good quality sleep, which may include a nap, with regular sleep and wake-up times.

Children and adolescents (5–17 years) should:

- Do at least an average of 60 min/day of moderate-to-vigorous intensity, mostly aerobic, physical activity, across the week.
- Do vigorous-intensity aerobic activities, as well as those that strengthen muscle and bone should be incorporated at least 3 days a week.
- Limit the amount of time spent being sedentary, particularly the amount of recreational screen time.

Measurement of physical activity

Domains of physical activity that are of interest include active transportation, school physical activity (including physical education, and activity during recess), leisure time or out of school activities, organized sports or sports clubs, outdoor play and domestic activities or chores. There are several valid and reliable measures of physical activity and sedentary behavior and the choice is largely dictated by the specifications of the research, domains of physical activity that are of interest, resources available and the training required. Accurate measurements of behavior are essential to understand physical activity in the growing child, including estimating population prevalence, identifying correlates, detecting trends, and evaluating the efficacy of interventions. In brief, common measurement tools can be categorized into self-report and device assessed. Although there are other methodologies such as direct observation and interviewing, that do not fit under these headings, they are beyond the scope of this chapter.

Self-report methods

Although device-based assessments of physical activity are becoming more popular, questionnaires are still the most frequently used globally, partly because they are perceived as having a lower cost and participant burden. There are many questionnaires available that have been designed specifically for use in children. Usually children, on average, are deemed to be able to complete a questionnaire by ~10 years of age. But given wide reading ages of children often assistance is required. An adult usually completes the questionnaire for younger children (e.g. via proxy).

Physical activity questionnaires can be classified as global questionnaires (short (often 1–4 questions) as part of a larger survey), short term recall questionnaires (from 7 to 20 questions/items and ask participants to recall, over the past 7 days or past month, on the frequency, intensity, duration of activities) and quantitative history recall questionnaires (recall physical activity over a longer period of time (e.g. one year, 10 years, across a lifetime)).[27] A review of questionnaires used in children and adolescents can be found in the excellent chapter by Hidding and colleagues.[28] Although self-report methods are useful for gaining contextual insight into mode (active transport, sports participation) and domain (school based, home based) of physical activity they risk overestimating and/or underestimating true physical activity energy expenditure.[29] The bias in estimates is due in a large part to difficulties in recall, social desirability (when children/adolescents or adults (completing via proxy) feel compelled to respond in a certain way) and the challenge of identifying or recalling sporadic, shorter bouts of unstructured physical activity.

Physical activity can also be self-reported via logs which ask a child, adolescent or parent/teacher to record discreet activities during the day. These can include checklists of specific activities that are completed at set times during the day (e.g. every 15 min) or at the end of the day. Physical activity diaries can be used to collect more detailed information (such as duration and intensities of activities, postures while performing activities, co-existence of behaviors, etc.). Physical activity logs or diaries have been found to be more accurate than questionnaires, likely because they do not require participants to recall behaviors.[30] However, log/diary completion is burdensome for the participants, and thus are often only used to collect data over a short period, e.g. 1–4 days which may not reflect weekly or habitual physical activity. Although using technologies, such as smart phones, has made the recording easier for the participant and the scoring easier for the researcher. Lastly, completing the information in real time could act as a motivator and this alter a child's usual physical activity – commonly referred to as reactivity.

Device measures

Accelerometers, and to a lesser extent heart rate monitors and pedometers, are commonly used devices for assessing physical activity. Pedometers are one of the most inexpensive and simplest devices to measure physical activity. Pedometers tend to be small, battery operated and most often worn on the waist. Although step-based ambulation does account for the majority of physical activity energy expenditure in children living without a physical disability,[31] pedometers are less able to identify steps accumulated in walking vs. running, or stair climbing and therefore compromises measures of physical activity intensity and are insensitive to non-locomotive and upper body activities. The latest generation of digital pedometers have time stamp data to estimate steps accumulated per unit time as a proxy of intensity.

Accelerometers are small electronic devices, that have time stamp abilities and are one of the most used devices for assessing free-living physical activity in children and young people. Accelerometers tends to be worn on the waist or wrist and are used in large representative surveillance studies of children and adolescents. Accelerometers measure the levels of accelerations in three orthogonal planes (anteroposterior, mediolateral and vertical) and raw acceleration is converted into an activity "count" over a user-defined time period of measurement (i.e. epoch). Activity counts are manufacture specific units and are converted into more biologically relevant units through applying intensity cut points (categorizing range of counts as time spent in a specific intensity (such as moderate or vigorous)). Accelerometers share challenges with the pedometer but also need sufficient consideration and training regarding data reduction (how to deal with different cut-points, epoch lengths, non-wear and sleep). Accelerometers tend to be more expensive than pedometers and, like pedometers, provide little information on the type or domain of physical activity. Hip worn accelerometers under estimate physical activity during cycling[32] and can mis-classify standing as sedentary time.

Heart rate monitoring is used to estimate energy expenditure and is based on the premise that there is a linear relationship between oxygen uptake and heart rate. It enables activity to be recorded over time and provides an estimate of intensity; however, as a method it is plagued with high levels of individual variability attributed to differences in children's biological age, gender, and fitness levels. Thus, most often heart rate sensors tend to be worn in conjunction with other tools to estimate physical activity.

Correlates

Identifying correlates of physical activity is essential to inform evidenced based interventions and is usually framed around a socio-ecological approach, that recognizes multiple domains of influence: individual, interpersonal, psychosocial, environmental,

policy and global factors. In addition to demographic characteristics, such as age (chronological and biological) and gender (which we will focus on later in the chapter), psychological factors have been well studied as a correlate of physical activity. For example, self-efficacy (a child's belief in their capabilities), self-concept (how a child describes themselves) and self-esteem are, among others, well established correlates of physical activity. Indeed self-efficacy has been shown to have a fairly consistent positive association with physical activity[33] and is the most often targeted mediator in published physical activity interventions,[34] although the evidence surrounding the effectiveness in school based interventions is mixed.[35] A meta-analysis shows that more active youth tend to display higher levels of self-concept[36] and that physical activity interventions lead to improvements in self-concept and self-esteem.[37] Psychological variables are both a correlate and an outcome of physical activity.

The interpersonal domain has also been widely researched and recognizes the importance of social relationships and cultural context. It tends to focus on the significant people in a child's life that exert influence over physical activity such as parents, teachers, and peers. Parental social support is a well-established correlate and important for initiating and maintaining physical activity. The types of support can vary but can be thought generally as tangible, instrumental (such as driving a child to a football practice), tangible conditional (such as playing with a child in a garden), intangible motivational (praizing a child for being active) and intangible informational (providing information).[38] Peer support is another important correlate as much of a child's physical activity is done with friends[39] and they perhaps become even more influential as a child moves through adolescence and becomes more autonomous. Peers can directly influence behaviors by co-participation and indirectly via praise and encouragement, sharing equipment and peer modeling, for example. Support from peers was most closely related to physical activity in 10−14 year old children compared with support from parents and siblings.[40]

The physical environment (natural and built environment) is an important part of the socio-ecological perspective surrounding correlates. Children and adolescents interact with multiple aspects of their physical environment, but certain aspects, such as the school-built environment may be more important than others with regards to physical activity. Urban design, and in particular the more walkable neighbourhoods are associated with greater active transport to school.[41] The most supported environmental correlates of physical activity for children have been identified as walkability, traffic speed/volume, access/proximity to recreation facilities, land-use mix, and residential density. The most supported correlates for adolescents are land-use mix and residential density.[42]

From a socio-ecological perspective, policies (laws, rules and regulations) are useful as they can change procedures and guiding principles, stimulate planning and redirect resources within an environment to target a change in behavior and within an institution (such as a

school) to shape the structure of programmes and curricular. Although evaluating the impact of policies on physical activity are challenging and findings are mixed, there is some evidence that targeted policies may have an effect. For example, the odds of schools delivering Physical Education increased in schools that were located in US states or school districts that had a law or policy requiring 150 min/week of physical education.[43]

Physical activity and chronological age

Much of the research on physical activity in young people has focused on those of school age children, with a predominance in the age 8−14-year range. Historically this may have been partly due to the assumption that pre-schoolers are innately active; however, the growing recognition of the importance of early years (e.g. the first 2000 days)[44] and the steep increase in obesity among this age group[45] has fueled more work in this age span. It is established that young children do not have the capacity for sustained activity and thus tend to accrue their activity sporadically and in short bouts of varying intensity interspersed with period of light activity and sitting. Active play is the most common physical activity in under 5 s and varies depending on the child's age/development (e.g. crawling, pulling up to standing and walking to more locomotor activities and object controls skills such as running, jumping and hopping).

During early childhood physical activity tends to continue to the unstructured including active play, which is fun, spontaneous, and volitional and in isolation or with other children. As a child ages there tends to be a move away from active play to more structure leisure activities, such as playing basketball with friends, and organized (team or individual) sports participation. Active transportation can also an important part of a child's physical activity.

Adolescence shows the most notable decline in physical activity and where gender differences in physical activity become more apparent (i.e. girls less active than boys).[46] This is partly due to the decline in unstructured and spontaneous activity (e.g. active play) which is an inevitable consequence of progressing to the mature state[47] and disengagement from organized sports and activities. Active travel becomes even more salient during adolescence where they might experience more autonomy and a wider roaming distance.[48] Explanations for the age-related decline on physical activity have largely focused upon psychological, social, and cultural factors, especially those that are deemed modifiable, (e.g. beliefs, motives, behaviors).[49] While psychosocial and environmental factors undoubtedly contribute toward the age-related decline in physical activity, there may also be a biological and/or genetic basis to this phenomenon.[50] That is, the decline in physical activity that accompanies late childhood and adolescence may result from underlying changes in biology and occur as natural and inescapable consequence of progress toward the mature (i.e., adult) state.[49]

Growth, development and physical activity

An often-uncontested statement made is that physical activity is essential for the growth and development of children and young people. While there is evidence that physical activity is important for the development of motor control, physical literacy, and cognition, its importance in relation to supporting growth and biological maturation is less clear. Certainly, there is no evidence to suggest that greater physical activity is related to enhanced stature (or an increased likelihood of reaching one's genetic potential for height). However, high volume of athletic training (and sometimes the stress and/or caloric restriction that accompanies it) has been linked, especially in the popular media, to concerns over stunted stature and/or delayed maturation in predominately female, esthetic sports such as gymnastics and figure skating. We will now discuss in more detail the rationale for and evidence behind the relationship between physical activity (including sport) and growth and biological maturity, and the direction of the association.

Does physical activity influence growth and biological maturation of a child?

The effect of athletic training on normal growth and biological maturation of female athletes is still a matter of debate. While it is generally accepted that physical activity and sports participation is an important part of childhood and adolescence, concerns arise when it is practiced intensively from an early age, and over a long period of time. Gymnastics is one of many sports in which, to be successful at the international stage, it is believed that training must begin before puberty and usually starting around 5–6 years of age with a peak in performance around 16 years. This means that elite female gymnasts undertake high volumes of training (e.g. 20–30 h week, all year) and competition from a young age.

Adolescent female gymnasts, on average, are shorter and less mature than other athletic and non-athletic populations of the same age,[51–53] which prompts the important question whether gymnastics training alters the tempo and timing of growth and biological maturation, resulting in reduced adult stature. To date a cause-and-effect relationship between intensive gymnastic training during childhood and/or adolescence and impaired growth has not been proven. Indeed, to answer this question, the effects of training on growth must be isolated from a genetic pre-deposition which requires a longitudinal study, controlling for the confounders of normal growth and sexual maturation. Most of the evidence base to date come from cross-sectional studies and are retrospective in nature. An exception are papers using data from the seminal 3-yr mixed-longitudinal Training of Young Athletes (TOYAs) study, initiated in 1987. Girls recruited from the UK Amateur Gymnastics Association into the TOYA study were significantly shorter than tennis players and swimmers at all ages, and were later maturing (i.e. attained menarche at an older age) but there were no difference in segmental growth (e.g. leg length to standing height

ratio).[54] The authors suggested that the reason for the short stature and the later biological maturity in gymnasts (and other female athletes) is that they are selected into participating in the sport most suited to their body size which is related to their maturity status. To support this conclusion, the correlation between age at menarche between athletes (including gymnasts) and their mothers who were athletes and between athletes and mothers who were not athletes were shown to the same as in the general population.[55] Thus, in summary, while there is still a need to scrutinize the impact of training (including psychological pressures and caloric restrictions), on child and adolescent athletes to ensure their safeguarding, the scant longitudinal data suggests that training does not alter the growth or timing of biological maturity in young athletes.

Does growth and biological maturation influence the physical activity of a child?

1. Active Play

Perhaps the best evidence for a biological basis to physical activity is in the study of active play. Defined as social or solitary, enjoyable, moderate-to-vigorous active pursuits that may involve symbolic activity or games with rules,[56] active play is the most common form of physical activity in young children and can be observed across cultures.[57] Active play is equally common among the young of many species, and has been documented and studied in dogs, cats, apes, mice, goats, and deer.[57] Given the opportunity, most children will naturally gravitate toward active forms of play, whether it be running, jumping, climbing, throwing, or engaging in simple chasing games such as "tag". Even when engaged in activities that are traditionally viewed as sedentary (e.g. talking on a phone, watching a television show) children often continue to move, whether it involve walking, pacing, dancing, or changing position.

Early theories of active play, such as the motor training hypothesis, argued that its evolutionary purpose was to optimize the development of physical, motor and social competence.[58] That is, through active play children can develop the necessary fitness, motor competencies, and/or psychosocial skills to operate effectively as adults. Although this explanation is intuitively appealing, it has been criticized in that these benefits are not exclusive to childhood and/or adolescence and can continue to be achieved in adulthood.[57] Rather, it has been suggested the true purpose of active play must reside in those benefits that are restricted to stages of childhood and adolescence. Benefits of active play that are exclusive to childhood and adolescence include cerebellar synaptogenesis and muscle fiber type differentiation. Synaptogenesis is a developmental process that involves establishment and refinement of neural synapses within the nervous system. The cerebellum is a major region of the hind brain that plays an important role in relation to motor control. Although it does not initiate motor behaviors, the cerebellum plays an important role in receiving

sensory input and integrating this information to fine tune motor activities (i.e. coordination, precision, timing). Research within animal models demonstrates that peak periods of active play coincide with the terminal phases of synapse formation and elimination within the cerebellum, yet decline afterward.[57] These observations would suggest that the function of active play in children may be the modification and refinement of specific brain structures associated motor control. This research also suggests that active play may be a biologically driven behavior that becomes redundant once specific developmental milestones pertaining to neural maturation have been achieved.[59] In support of this contention, active plays has been shown to decline with age in British boys and girls, even among those who maintain the recommended guidelines of 60 min of moderate-to-vigorous physical activity per day.[60]

2. Gender differences in physical activity

As previously mentioned, it is consistently shown that boys, on average, are more active than girls at each age. However, when physical activity is aligned to biological age (e.g. years from age at peak height velocity) rather than the traditional chronological age, the gender differences in physical activity disappears.[61,62] A similar finding has been shown for sedentary behavior.[63] Thus, maturity differences between genders (i.e. on average, girls mature earlier than boys) may be one reason why research consistently shows that girls are less active than boys of the same chronological age. It also adds some evidence, albeit not causal, to suggest that biological maturity may impact physical activity in adolescents. It should be noted, however, that most of these studies have employed estimates of somatic maturation and that the associations between maturation and sedentary behavior may vary across different biological systems.

3. Biological maturity timing and physical activity/sports participation

A recently published systematic review[64] examined the evidence surrounding the association between maturational timing (i.e. early, average and late) and physical activity (including sports participation and active travel) and sedentary behavior in adolescents. The review identified 64 unique studies, that met the inclusion criteria. An inverse relationship between maturational timing and physical activity was found in 60% and 50% of studies (for boys and girls, respectively) and a positive relationship between maturational timing and sedentary behavior (in 100% and 53% of studies (for boys and girls, respectively)) was found. Less evidence was available to support an association between maturational timing, sports participation, and active transportation. The authors suggested that the inconsistency in the findings may be due, in part, to varied indicators and/or measures of biological maturity (crossing both somatic (prediction and attained), skeletal and sexual) and outcome measures of physical activity and sedentary behavior.

The timing of maturation, and in particular the onset of puberty, has been shown to differentially impact sport participation in boys and girls.[64,65] Girls who mature in advance of their peers are disproportionally represented in the majority of sports programmes, with the exception of tennis and swimming where greater size and/or strength may afford an athletic advantage.[65] This disproportionate representation of early maturing girls coincides with the onset of puberty and typically increased in magnitude with age. Early maturing girls are especially underrepresented in sports that involve endurance and esthetic qualities, such as dance, ballet, gymnastics, and diving.[66] Although early maturing girls tend to be underrepresented in many team sports such as soccer, netball, and basketball, the extent to which this bias exists is largely dependent upon the trade-off between physical, athletic, and technical and tactical aptitude. That is, superior technical, tactical, or psychological abilities may compensate for any physical or functional disadvantages associated with earlier maturation.

The timing of maturation has also been shown to impact boys' participation in organized sports.[65] In most male sports, and especially those that demand greater size, speed, strength and/or power (i.e. rugby, soccer American football), there is a selection bias toward boys who mature in advance of their peers. As with girls, the maturity bias in boys emerges at the onset of puberty and generally increases in magnitude with age. This bias is especially pronounced in professional sports academies and national junior teams where there is added pressure to win and thus field the most able athletes. A recent study of maturation and player selection in youth soccer players from the Manchester United and Aspire academies demonstrated that from the under 16's to under-17's age groups between sixty-to-eighty percent of all boys could be categorized as being early maturing (i.e. having a skeletal age of at least one year in advance of their chronological age), whereas late maturing players made up only two to three percent of the sample.[67]

While the athletic advantages afforded by variance in pubertal timing may directly impact physical activity and/or performance and fitness in a sporting context, it is important to recognize that they exist in a socio-cultural context. The child's perception of change, their values and beliefs pertaining to growth, maturation, sport and physical activity, and the reactions and evaluations of others are as, if not more, likely to shape their behavior in active domains. Perceptions of the physical-self have been shown to mediate the relationship between early maturation and reduced physical activity in adolescent girls.[68–70] That is, girls who mature earlier generally perceive themselves as less attractive, less physically fit and athletic which, in turn, predicts less engagement in physical activity. Conversely, early maturing girls that perceive high levels of peer support are just, if not more, active than late maturing girls.[71] The results of these studies are encouraging in that they suggest that early maturation need not serve as a risk factor or barrier toward participation in physical activity among girls. They also suggest that by encouraging girls to view and accept the changes that accompany puberty as natural and

attractive consequence of progress toward womanhood, (and not barriers to physical activity), they may be less likely to become inactive through this stage of development. Likewise, girls should be encouraged to both accept and support each other through adolescence to help maintain active behaviors.

Boys who mature early tend to hold more positive perceptions of their physical selves than their late maturing peers.[72] Perceptions of physical and/or athletic competence have been shown to predict motivated behavior in sport and physical activity and thus may explain why early maturing boys are disproportionally represented in many sports.[73] On the basis of their physical and athletic advantages, early maturing boys may also receive greater encouragement and reinforcement to engage in sports.[49] Although there is limited evidence on the social management of puberty in the context of sports, there is emerging evidence to suggest that early maturing boys are perceived and evaluated by coaches as being more physically competent and having greater athletic potential.[74,75] Although late maturing boys are under-represented in sports programmes as adolescents, they do appear to remain as active as their early maturing peers. It is possible, that late maturing boys participate in alternative active pursuits such as recreational cycling, skateboarding and/or active play. Future research should be conducted to explore and better understand the social management of puberty in the context of sport, with particular emphasis upon the roles of peer, parents, coaches, and educators.

4. Relative age effect

The relative age effect is a well-documented phenomenon whereby the children who are the oldest within an age cohort are more likely to succeed and/or be represented within achievement domains.[76] For example, male academy footballers born within the first three months of the selection year in England (September, October, November) are disproportionally represented in comparison to those born in the three months at the end of the selection year (June, July, August). The relative age effect can be observed from early childhood in boys[77] and remains relatively steady through early-to-mid adolescence before experiencing a slight decline in late adolescence and early adulthood. Relative age effects are less common in girls' sports, though may be more apparent at the highest levels of competition. Contrary to lay opinion, relative age is not synonymous with maturation. Rather, relative age and maturation are independent constructs that result from different factors and emerge and operate independent of one another.[67] Relative age is determined by date of birth and the criteria for inclusion within a selection year and its variance within age groups competition is generally limited to one year. Maturation, in contrast, is determined by a combination of genetic and environmental factors and can vary by as much as five to six years among children of the same age. As such, it is entirely possible for a child to be the oldest, yet least mature, athlete within his or her age group, and vice versa. Research in academy soccer suggests that relative age and maturation are at most, weak-to-moderately

associated with one another, with maturation explaining about nine percent of the variance in relative age.[78] The independent nature of these constructs is further illustrated in the ages at which their associated biases emerge.[79] Whereas relative age effects can be observed from early childhood and remain steady through adolescence, maturity selection bias emerges at the onset of puberty and increase in magnitude with age. The fact that relative age effects are also observed in non-physical domains such as education, business, and politics underlines the fact that the mechanisms behind this phenomenon are more likely to result from age related differences in experience and/or cognitive, motor or social development, than maturation. Accordingly, strategies designed to counter relative age are unlikely to impact maturity associated selection biases and vice-versa.

Biological maturity and growth-related injury risk

As noted, participation in sport is generally considered to contribute positively toward physical and psychological development in youth. The adolescent growth spurt is, however, recognized as a stage of development where there is an increased risk for and prevalence of overuse and/or growth-related injuries.[80] Such injuries are especially prevalent among young athletes who participate in sports or activities that demand greater volumes of high intensity training, load bearing, frequent accelerations and decelerations, and repetition. Overuse and growth-related injuries account for between 15 and 30% of all emergency department musculo-skeletal injuries in adolescence, with 40% of acute case being sports related. This is not that surprising as during the growth the apophyses, epiphyses, and articular surfaces are less resistant to tensile, shear and compressive forces than pre-pubescent or mature bone, due to the lack of collagen and calcified tissue.[80]

Evidence suggests that there is a marked increase in injury incidence and burden among athletes as they enter and during the adolescent growth spurt.[81–83] These risks may be greater for athletes who mature later than their peers as they will experience the growth spurt at later ages when training volumes and intensities tend to be higher. Misty Copeland, the first African American to attain the role of principal dancer at the American Ballet experienced delayed onset of puberty and thus experienced her growth spurt much older age than her peers. During this phase of her development, she experienced multiple stress fractures in her lower limbs, ankles, and lower back during this phase of her development; forcing her to temporarily cease dancing to recuperate. The risk for specific types of injury may also vary relative to the athlete's stage of maturation. Research in academy football demonstrates that growth related injuries tend to cluster around the growth spurt, with the onset of specific types of injury reflecting the distal-to-proximal growth axis.[84] Sever's disease, for example, tends to occur at the onset of the growth spurt reflecting the fact that growth occurs in the foot prior to the lower limbs. In contrast, Osgood's Schlatter's disease is more likely to coincide with the peak of the growth spurt

when growth in the lower limbs is at its greatest. Finally, growth related injuries in the hip and lower back are more likely to present during the latter stages of the growth spurt or within the deceleration phase.

Through the regular assessment and monitoring of growth and maturation, and consideration of related factors such as training load, content and symptomology it may be possible to reduce the incidence and burden of growth related and overuse injuries in youth.[80] Jan Willem Teunnisen, a proponent of the Athletic Skills Model and a former movement scientist at Ajax FC, describes a strategy to better manage, and reduce injury through the growth spurt in adolescent footballers.[85] This strategy involved the modification of training load and content as players entered the growth spurt. Specifically, these modifications involved a reduction in training load and activities that involved a significant amount of acceleration and deceleration, coupled with a greater emphasis upon skills that develop coordination, balance, core strength, mobility, and the re-training or fundamental and sport-specific skills. Applying these principles across a competitive season, sports scientists at AFC Bournemouth reported a 72% reduction in time loss injuries among academy player that were identified as being within the pubertal growth spurt.[86] Although these findings are encouraging, further research is required to better understand the mechanisms and processes underlying these benefits and the most appropriate training load and content to reduce injury risk and burden through the growth spurt.

Emerging areas

Bio-banding

As part of the Elite Player Performance Plan (EPPP), the English Premier League (EPL) implemented a league wide "Growth and Maturation Screening Program", assessing the growth and maturity status of over 3000 registered academy players in England and Wales.[87] To support this initiative the EPL and Football Associations developed and implemented accompanying educational programmes on the importance and assessment of growth and maturation in youth football for coaches and sports science and medicine staff. Working with academics from the University of Bath, the EPL developed and integrated a growth and maturation module within their "Player Management Application"; a performance and data management system that monitors all players in Premier League and Category one academies. The new module affords more reliable and accurate assessment of growth and maturity and is routinely used to[1] assess growth and maturation status,[2] generate and access on-demand player and team audit reports,[3] group players by maturational bands for training/competition (bio-band),[4] inform training design and prescription,[5] evaluate player fitness and performance relative to age and maturational standards, and[6] identify developmental stages associated with greater injury risk (i.e. growth spurt).

Recognizing the impact of maturation upon athletic performance and competitive equity, the Premier League also introduced the concept of bio-banding within their academy games programmes. In bio-banded competitions, players are grouped within maturity "bands" rather than age groups. The purpose of this strategy is to limit maturity associated variance in size and function, promote competitive equity, and present early and late maturing players new lew learning experiences and challenges. Preliminary evidence suggests that bio-banding changes match demands, placing greater emphasis upon technical and tactical over physical aptitude.[88–92] Bio-banding also appears to differentially benefit both early and later maturing players. Competing against older yet physically matched peers, early maturing players are unable to play to their physical and functional advantages and must employs technical, tactical, and psychological solutions to succeed. The process of "playing up" (i.e. competing with older players) also encourages early maturing players to aspire to match, and learn from, older and more experienced players.[93] In contrast, older later maturing players have more opportunity to command the game, take on positions of leadership, and both utilize and demonstrate their technical and tactical attributes. Late maturing players also could consolidate the learning through the mentoring of their younger early maturing peers.

Bio-banding can also be used to group players for training and conditioning programmes. Practitioners have long recognized the importance of accommodating individual differences in growth and maturation when designing,[85,94] implementing and evaluating conditioning programmes. Allowing for experience and technical competence, young athletes should be grouped by maturity to optimize training effects and ensure mitigate injury risk. In childhood, for examples gains in strength, speed, and power are best achieved through activities that promote adaptation of the neuromuscular system, whereas post puberty such gain can be achieved through a combination or structural (i.e. hypertrophy) and neuromuscular adaptation.[95] As previously noted, training and conditioning programmes may be adapted during periods of growth acceleration to enable athletes to better adjust to the rapid changes in size physique and function that accompany puberty, and to mitigate the risk of overuse or growth-related injuries.[85]

Bio-banding principles should also be applied to the processes of talent evaluations to better account for individual differences in biological maturation. As previously noted, the Premier League's PMA allows practitioners to evaluate the fitness of academy players relative to their age and maturity specific standards.[87] It is possible to adjust player match grades relative to the players status within a competition, allowing coaches to evaluate how well players performs when they are one of the most and least mature players within an age cohort.[96] Such strategies may be particularly valuable in relation to the scouting of players and in terms of informing decisions pertaining to whether a player is retained or released from an academy.

Physical activity interventions

To date, there have been a number of published interventions that have focused on adolescent girls (e.g. Girls Active,[97] Project TAAG[98]). We do not see the same focus on boys. A primary rationale that is often cited is that girls are less active than boys. However, as previously mentioned, this could be explained by boys entering puberty on average 6–12 months after girls. While there is rationale to support gender-targeted physical activity interventions, because of the known gender difference in activity preference, correlates and barriers to PA,[99] it may be misguided to target resources to adolescent females over males. It may be that interventions need to target girls earlier in adolescence and boys later in adolescence.

A future area of research is to investigate the design and implementation of interventions to consider variation in timing of biological maturity within and between genders. Many school-based interventions are based on chronological age groups (i.e. grades) in schools. This is understandable as they are easier to implement and keep friendship groups together. However, within one grade, there is considerable variation in biological age and in the level of biological maturity attained. That said, one must acknowledge the potential hurdles in conducting targeting adolescents of a specific maturity status. For example, targeting early maturing girls, for example, would likely be challenging approach, adolescents may be more comfortable participating in interventions with their peers in the same grade. Also, considering that most school scheduling is based on chronological age grades, organizing maturity-based interventions that span many grades may be problematic.

Conclusion

Physical activity is essential for the health and wellbeing of children and adolescents and a concerted effort is needed to help children and adolescents overcome their hypokinetic environment and remain active into adulthood. In addition, to other important correlates/determinants, variation in biological maturity likely plays a role in adolescent disengagement from physical activity and certainly impacts selection and sporting performance among adolescent athletes. The measurement of biological maturity in the field settings remains a challenge and the lack of standard measures and/or harmonization of physical activity and biological maturity data hinders comparison across studies/populations. Future research needs to investigate the various mechanisms and processes through which these associations between biological maturity and physical activity occur, how individual differences in maturation and development are best managed in a sporting context (including injury prevention), and the extent to which these processes may also impact general engagement in physical activity.

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Suggestion for further reading and websites

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CHAPTER 18

Biological models of human growth

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Introduction

How, exactly, the wide range of adult sizes found among human populations[1,2] arises as the growth process unfolds from the incipient first cell is an active science. How we grow is both one of the most exciting areas of research in human biology and one of the most troublesome in knowledge limitations regarding specific mechanisms. This is a pressing need as it has become increasingly clear that how well our bodies are built in the earliest years has an impact on lifetime health.[3] New knowledge about human growth is no longer limited to a focus on how it can inform our treatment options and interventions for abnormal or less than optimal childhood growth. Defining how the body grows is now fundamental to prevent and pre-empt chronic disease, and support cellular health across the lifespan. Seeking clarity in the mechanisms by which earliest growth contributes to developmental origins of health links basic molecular and cell-level scientific research to best-practices in the service of both clinical medicine and public health. Numerous challenges confront the science of human growth: How can we best contribute to building a healthy body to last a lifetime? What is it about cellular processes that influence this? How can we best understand body size as a marker for nutritional intervention efforts globally? How should we proceed to treat short stature without driving adipose tissue deposition? Could we be better informed in our attempts to support preterm infants? Answering these types of questions relies on our understanding of the basic determinants and physiology of growth.

This chapter considers biological models of human growth. A growth model is a schema that purports to describe how growth occurs. Model accuracy is important to support successful practices aiming at improving individual's lives. The closer the model approximates biological reality, the more likely it is that productive interventions can be designed. From a model that envisioned a preformed small human homunculus in the Enlightenment to the search for genetic predictors in modern times, models of human growth biology both benefit from and are limited by historically-situated scientific knowledge and practices. In recent decades, some models that have been assumed to reflect

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growth biology are derived from statistically-based descriptive graphics of infrequently measured children's size at various ages. Other models derive from empirical evidence gathered from serial measurements of the same children across time. This chapter proposes that understanding growth biology is best driven by data documenting growing children measured frequently enough to capture growth itself, in lieu of inferring how size changes occur on the basis of visual and statistical models or graphic interpolations.

Human growth: building a body is a cellular job

The most notable feature of early human development is the change in size and form that occurs as one cell becomes a fully-developed newborn across approximately nine months, and the continued increase in size thereafter. Building a human begins with a zygote, the newly formed cell comprising genetic material from both parents, as a membrane-bound unit of roughly 100 μm in diameter and 0.004 mg in weight.[4] Approximately 270 days later, this initial cell gives rise to a fully-formed human infant at a range of sizes,[5] influenced by numerous genetic and environmental factors, as well as the duration of the pregnancy. For reference, birth before 37 weeks is considered "early," or pre-term, and beyond 42 weeks is considered "late." Prior to birth, the original one hundred micron zygotic cell undergoes a complex fetal growth journey to construct the neonate.

It is important to note that the word "growth" is often used very broadly and without precision, as it is here, in the phrase "fetal growth." Growth literally means an increase in size, which in living things reflects both increasing cell numbers and cell sizes. The emergence of the neonate from the zygote, however, represents far more than simply an increase in either cell size or cell numbers. The newborn is the result of the highly-organized dual processes of growth and development, or processes of cell division followed by cell specialization, spatial localization and functional activation. A biological model of growth must account for a mechanistic integration of this coupled system. A nonspecific "increase in size" concept, derived from the fact that children get bigger across age, is an insufficient framework within which to work toward answering specific questions about how variability in size occurs and how to influence this.

It has long been understood that growth and resulting size reflect environmental conditions.[6] Beginning in the latter half of the twentieth century following new discoveries in genetics, the search for how children grow to become relatively "short" or "tall" became focused on the principle that "size" and "growth rate" reflect genes interacting with the environment. Large-scale studies aimed to quantify the relative contributions of genetics and environment to height growth, with height heritability,[7] or the proportion of total variance explained due to genetic factors, estimated at between 20 and 62% in different investigations.[8–10] This wide range has been attributed to methodological differences across studies (e.g., sample size, stratification, nature of the data and genetic

variants) as well as the complexity of environmental influences. While no simple answer regarding the predictive magnitude of specific genetic variants on human height emerges,[11] studies have provided evidence for a more nuanced understanding of how cells translate genes and environmental influences into form.

Among the gene variants reported to have statistically significant height associations are those coding for proteins involved in pathways with biologically relevant growth-related cellular processes (mTOR, fibroblast growth factors, WNT/β-catenin, for example).[9] The functionality of these proteins is highly influenced by the nutritional, energetic, and stress-related stimuli within the local environment of long bone growth. The fact that there are feedback loops between both the gene products related directly to cellular growth and those that function as environmental signals, makes clear that aiming to disarticulate genetic from environmental effects is not the right approach. Instead, an integrated understanding of the mechanisms by which these proteins and cells collaborate provides a more useful frame for assessing the regulatory points underlying attained height. It is becoming increasingly clear that variation in form is the outcome of cells building structural components and influencing metabolic systems as part of a dynamic functional network established in support of mediating genomic adaptation to environmental resources.[12] A robust model of human growth must explain how the environment is translated into morphology by way of cell level activities across systems, organized by hierarchical nodal decision points.

Genes and environment engage from earliest development in nexus sequences. The body is built as cells arise from previous cells during mitotic activity points in the cell cycle.[13] In order to create two new cells with exact duplicates of the original genetic material and properly apportioned cell contents, a series of carefully orchestrated chemical processes take place. Under normal circumstances, the proliferative events of cell division punctuate periods of quiescence or dormancy, when no cellular division occurs. Cells divide when they receive a chemical permission signal to do so, a decision significantly influenced by resource availability in terms of both energy and building blocks.[13] In this way, growth is matched to available resources, and organism integrity is preserved by preventing uncontrolled over-growth—or cancer.

As new cells are produced, some remain dormant, awaiting further instructions on what each may become − we call these stem cells, named for the fact that they can become any part of the developing organism.[14,15] Stem cells are sequestered in niches around the body where the microenvironment favors their health − areas of low oxygen in the bone marrow, for example.[15] Here, they form a reserve supply for replenishment, available to be called upon as needed in the regular wear and tear of cells with short lifespans (skin cells, blood cells, immune cells, for example), and to repair the body across age. Other stem cells are called upon as the source for organ construction and integrity during

development. At genetically-determined times, cellular destinies are initiated as specific genes are activated and protein-mediated sequences determine cell proliferation and differentiation events. A number of organs complete their architectural construction prior to birth, developing all the cells they will have to function for a lifetime (e.g., kidneys, skeletal muscle, heart muscle, a considerable portion of the brain, for example).[16,17] Other organs retain stem cell potential and critical periods for structure and function growth and development continue into postnatal life (bone and immune cells, for example).[15]

These details expand our understanding of "growth" to acknowledge that emergence of the organism as an increase in size represents specific collaborations among chemical networks to coordinate both the timing of cell divisions, and therefore number, and the subsequent cellular differentiation sequences responsible for the shapes and forms that determine the architecture and functionality of the human body. Both cell division and differentiation are influenced by available resources. In this way, through its formative effect on structure, growth has a fundamental influence on function, and therefore, health. While it is logical that a growing organism's growth is restricted by energy resources and lack of available building blocks, it is important to understand how, *exactly,* this happens. The answer is found in the workings of the cell division process phase of a cell's life cycle, and in the differentiation pathways that follow.

Both cell division and differentiation are controlled by chemical gates that assess energy and protein, and both are inhibited until permitted to progress.[13] Clarifying that growth biology is a start and stop process is fundamental to understanding how individuals grow and how growth plays a central role in the origins of health.

Growth in nature

The natural world provides excellent examples of growth biology. Plants negotiate their growth and survival daily as chemicals constantly monitor the environment, permitting plants to adapt their cell divisions, differentiation and size expansion to changing environmental conditions.[18,19] Plants do not grow continuously.[20] Chemical activities both promote and inhibit growth, by way of mechanisms that include direct inhibition of gene expression and cell activity, and the release of this inhibition.[21,22] Trees from temperate latitudes transition between growth and dormancy in an annual cycle. Dormancy is characterized by the cessation of cell divisions and reduced metabolic activity. This is achieved by way of chemicals that respond to temperature and to light, monitoring the daily photoperiod. As days become shorter each fall, protein synthetic changes occur that result in growth cessation, leaf shedding and dormancy. As days become longer and temperatures increase each spring, specific genes responsible for the timing of bud emergence from dormancy are activated. These genes control protein activities that influence cell division rates and synthetic activities in different plant segments.[22,23] Not

only is the primary growth of plants, or their height, evident in the annual cycle associated with limb length and leaf production, but their secondary, circumferential growth follows this cycling as well. This is recorded in their structure and appears as tree rings. Particularly evident in climates with hot summers and cold winters, the rings mark the growth and dormancy transitions, with early growth pushing the bark outward and growth cessation reflected in the dark, denser areas seen in cross-sections of tree trunks, where the history of growth cycles are embodied. The importance of temporal transitions between growth and dormancy to size may be best exemplified by bonsai trees. Genetically identical to trees of the same species that are full-size, it is the duration of dormancy that is responsible for their miniaturization. The small size is the outcome of only rare releases of growth inhibition, permitting limited cell division and differentiation sequences.

Animal growth biology follows a similar pattern of growth and dormancy, albeit decoupled from a reliance on seasonality among species. Studies among fish, rabbits, rats, dogs, sheep and humans have documented that bones grow in bursts during short time intervals of minutes, separated by intervals no growth.[24–27] Observable in both serial ultrasounds on the human fetus and anthropometric measurements taken on head circumference and length/height postnatally, children grow in spurts – separated by intervals when no growth occurs.[28–30]

Saltation and stasis: how children grow

Identifying the pattern by which children increase in size (grow) turned out to be a signal-to-noize problem, common among digital systems, or those that function according to on/off signals. When individuals are measured with sufficient frequency, increments in skeletal size are evident as unique time-constrained growth events that interrupt durations of no growth. Following the vocabulary for similar biological processes previously identified in neural tissue, this growth pattern has been labeled *saltatory*, and the unique growth accretions, *saltations*.[29]

These saltations were originally identified in humans when the total body length of infants was measured daily.[29] At observations within this time frame, careful measurement techniques identify unique growth increment events that stand out by contrast with surrounding time intervals when no growth, or increase in size, occurs. These intervening time durations of no measurable accretion, or *stasis* in terms of incremental growth, separate the individual growth saltation events. Thus, growth in size can be visualized as a stepwise function, with pulsatile increases in size resulting in unique steps of variable heights (Fig. 18.1).

For example, in infancy, total body length/height increments range from 4 to 20 mm during 24 h, while head circumference saltations most commonly range between 2 and

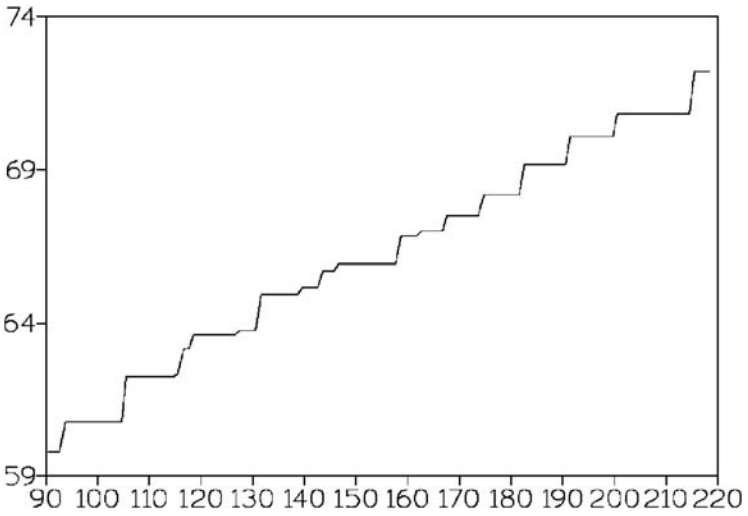


Fig. 18.1

The saltation and stasis growth pattern from daily data (day of age, *x*-axis) of total body length measurements (cm, *y*-axis). The subject was a male infant followed from 90 to 218 days of age. These data were obtained after parental informed consent under a University of Pennsylvania approved human subject protocol. Twelve statistically significant growth saltations contribute to the total growth during the interval. These occur at days 93 (0.98 cm), 105 (1.47 cm), 116 (0.81 cm), 118 (0.46 cm), 131 (1.2 cm), 143 (0.55 cm), 158 (0.92 cm), 167 (0.5 cm), 174 (0.68 cm), 191 (0.91 cm), 200 (0.72 cm), 215 (1.39 cm). Thus, total growth was accrued on 12 days when variable amplitude growth saltation occurred after intervening stasis intervals of 2—16 days.

3 mm in 24 h.[29,30] In our data, saltations are separated in time by intervals ranging from one to more than 60 days, when no measurable growth occurs. Intervals of no measurable increment vary both within individuals and between individuals.[29] Developmental age is important: Individual children have more frequent saltations when they are infants and adolescents than during mid-childhood.

The bases of a "growth clock" have yet to be clarified. Analyses to date provide evidence for growth saltation timing as aperiodic (separated by unequal dormancy intervals) but nonrandom, suggesting that the growth process is an expression of a nonlinear dynamical program.[31,32] This provides enormous flexibility for a biological system: Like plants, this *saltation and stasis* growth biology permits individuals to modify their growth according to environmental conditions, sometimes waiting to grow until conditions improve. If the no-growth state is prolonged, growth stunting may result. In some organs, such as bone, as conditions improve individuals have the possibility for a recovery by means of a short-term increase in the frequency or amount of growth to "catch-up" on what they temporarily lost. Bone growth opportunities extend until the end of the developmental

period, when the bone growth cells at the growth plate are depleted and adult height is achieved. Catching-up is not possible for all organs, like the heart, kidney, skeletal muscle, and parts of the brain, in which all cellular proliferation is completed before birth.[16,17]

A paradigm shift in growth models

It is said that often in the history of science, everyday observations lead to common knowledge about events that precede scientific discovery of these same occurrences by many years. Human growth exemplifies this. The parents of the children in these studies often state that their grandmothers knew perfectly well that children grow in spurts, and they ask how it is that scientists need to study something so obvious.

The fact is that scientific documentation of day-to-day growth patterns is uncommon. The history of human growth science has been characterized primarily by the interests of both clinicians and public health workers, in order to answer questions on the nature of "normal" development, and define when interventions are necessary. In addition, data collection from populations globally has been important to understand the range of variability by which individuals make the journey from earliest ages to the achievement of adulthood. These studies have relied on measuring children at relatively infrequent intervals. Most often, these have been annual and semi-annual time frames, aiming to document the variable sizes and shapes of populations representing diverse gene pools, residing in a variety of ecologies with different histories. The resulting data have provided the basis for the commonly used growth reference charts illustrating percentile distributions of size-for-age.[5] The growth chart concept aims to provide clinicians and public health professionals with a reference by which to assess "normality" of an individual's growth progress. Growth curves emerge as tabular data are transformed either by a graphical-fitting procedure or the application of a curvilinear or nonlinear mathematical function to sequential annual, semi-annual or monthly measurements, sorted by size-for-age percentiles. This approach interpolates size between actual data measurement time points, to provide a general description of the fact that children get bigger with age, useful for gauging children's size-for-age compared to their peers.[33]

Many different growth charts have been devised that are distinguished by the sample according to historical time, geographic locale, feeding strategy or subject's clinical status (among other variables). A traditional anthropological focus on describing variability among population growth patterns has been challenged by a universalist view that diversity in growth patterns is actually a documentation of compromised growth, and offers growth *standards* purporting to represent an optimal size-for-age goal for all children worldwide.[5]

Regardless of their intent or use, the graphic image presented by the growth curve models became accepted as a model for the biology of growth—a continuous model of daily growth.[34] While the "size" data determining the curve's specific features are actually predominantly interpolations between actual data points, and the form is an artifact of applying mathematical equations that assume a continuous function, visual inspection of growth curves implies that growth occurs little-by-little each day. Growth rates have been estimated from mathematically-calculated first derivatives of the curves (point estimates of rate as change/time). Simply summarized, the science of human growth has been characterized by investigations of imputed and derived variables statistically modeled by approaches that assume, and therefore impute, a view of continuous human growth.[33–35] Notably, the growth curves and subsequently derived theoretical models of growth omit the fundamental reality that growth of most living things is a biological system of growth and dormancy. The derivation and adoption of the continuous model of growth is an understandable assumption based on the methods of the time. As most children grow within the traditional measurement intervals, it was not possible to know that the apparent continuous trends in size across time actually reflect an underlying process of discrete growth events, insufficiently sampled. Only more frequently collected data can reveal the actual timing of growing, and identify a nonlinear and discontinuous, saltation and stasis process.[36]

The emergence of the saltation and stasis model

In order to identify when children actually grow, and characterize the pattern of growth timing, studies require careful attention to measurement timing protocol, data acquisition technique with assessment of measurement error, and methods of data analysis.

Measurement protocol

In order to begin to understand the underlying biological mechanisms that drive the growth process, it is necessary to conduct a time-intensive longitudinal study, following the growing organism at high frequency intervals, so that growth can be isolated as an object of study. The best measurement interval for capturing a growth saltation was not known prior to the studies described here. Fundamental in designing a study aimed at elucidating the growth process is the sampling protocol. A measurement frequency must be chosen that will provide adequate data in relation to the timing of the underlying growth events.[36] This is not always known in advance. Pilot studies are essential: The investigator chooses an initial window for sampling and reiteratively tests the time frame.

As an illustration, Fig. 18.2 presents infant growth data as it appears collected at monthly, two week, weekly and daily intervals.[36] These different amounts of information lead to

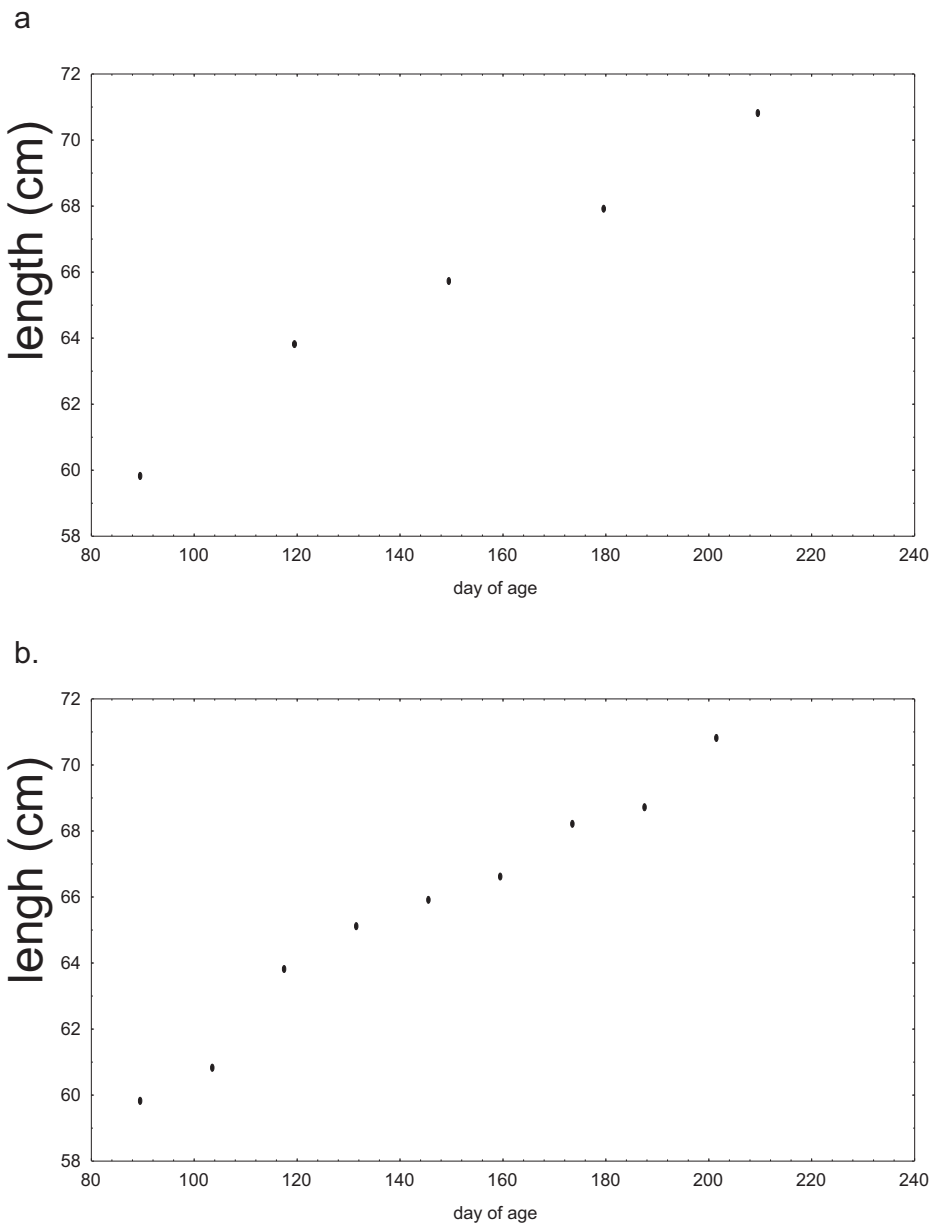
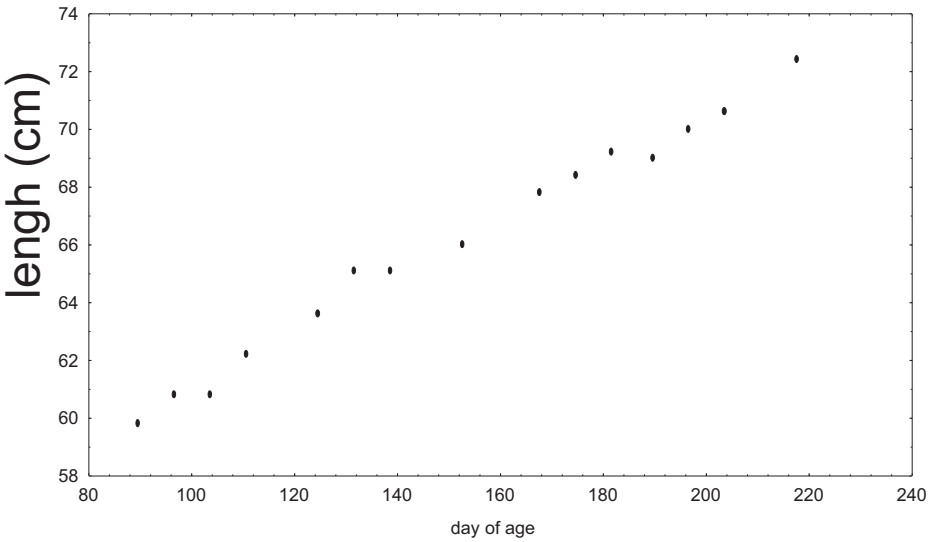


Fig. 18.2

The effect of measurement interval on growth pattern identification. The experimental data from the infant described in Fig. 18.1 are represented in four time frames: (A) data at 30 day intervals, beginning on study day one; (B) data at 14 day intervals beginning on study day one; (C) data at 7 day intervals beginning on study day 1; (D) a subset of daily data from study day 1–73, for clarification of the growth pattern lost by less frequent measurements.

c.



d.

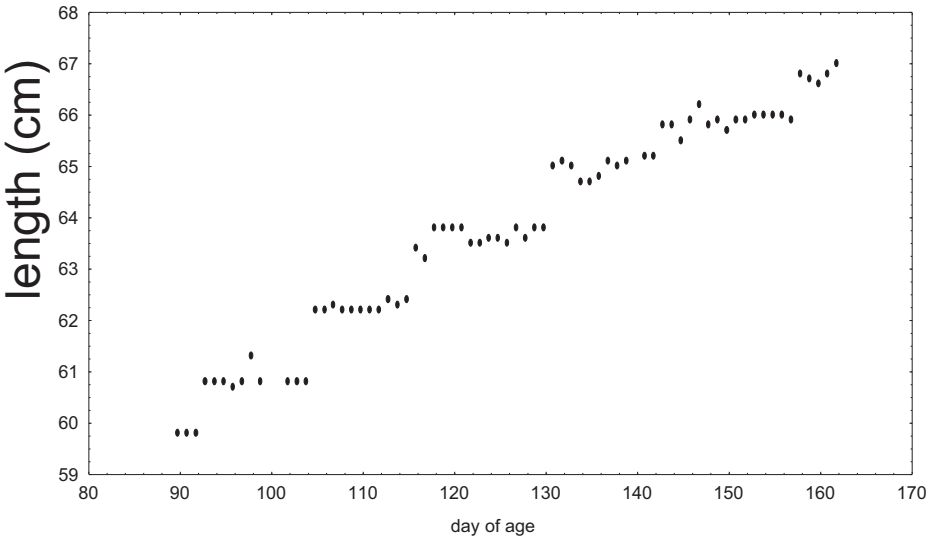


Fig. 18.2
Cont'd

quite different inferences regarding the underlying growth biology in this individual. All of the time frames identify growth as a process of increasing size across time. They differ significantly as data density increases, inferring different models of growth. If one has only data collected monthly (Fig. 18.2A), it is impossible to know anything more than that

there has been a trend to get bigger over the course of the month. One might guess that a continuous line would be a reasonable approximation of the path taken by the biological process between data points for Fig. 18.2A. A researcher might be tempted to connect the points and be satisfied that we understand, approximately, how this individual grew during this time interval. Simply drawing a connecting line between the dots, however, symbolically states that growth occurs each and every day between the points, at a relatively constant rate each day. This is an approach often employed in growth studies. Once such lines are drawn, they are used for deriving daily growth rates from the slope of the equation for the line.

As the timing between measurements is reduced, it becomes clear that this linear proposition might not be the real or best description of how this individual is actually growing in length throughout the study interval. Data collected at two-week intervals (Fig. 18.2B), suggests a continuous, if nonlinear, process – or growth characterized by changing rates. Weekly data collection (Fig. 18.2C) suggests this might consist of an organized nonlinearity, with some dormancy intervals. Data collected daily clarify a stepwise pattern as the underlying growth trajectory (Fig. 18.2D.

What is clear from this exercise is that with less frequent data, one cannot accurately identify a saltation and stasis process between two data points. With insufficiently frequent data points, the distinction between a dormant period of no growth is lost and the specific timing characteristics of growth are unresolvable. This example illustrates that growth data analysis presents problems similar to the challenge of a connect-the-dots diagram in which the precise path becomes clarified only with increasing dots. The issue for the researcher interested in identifying the growth process is to collect sufficient information with which to reconstruct the biological process by which increase in size actually occurs. For a saltatory process, data density is important to identify durations of dormancy and more precisely identify the temporal patterns of growth—when it starts and stops.

Measurement error considerations

There is a second problem confronting the researcher when making a decision regarding measurement frequency: No measurement is free of error and certainly no human growth measurements are exempt from this consideration.[37] The sources of error at each measurement point reflect the precision of the instrument to accurately measure an object, the manner in which the object is measured, and any endogenous physiology that might contribute to variability in actual size. Thus, scientific study of saltatory growth requires consideration regarding the technology employed, the researcher's ability to take the measurement and the state of the subject.[38]

In order to clarify the time window of observation for a study, it is necessary to conduct a pilot study to identify the actual measurement error of the particular observer and the subjects to be studied, and to compare this measurement error with the incremental process under study. If biological increment and measurement error are equal, it would not be possible to identify changes in the data series due to biology from error. This is an often-unappreciated reality of time-intensive investigations. In general, saltatory increments follow the general principle of identifying signal from noise, and must be at least twice the technical error of measurement associated with data collection to be identifiable from error.[39]

Moreover, the longitudinal nature of a time-intensive growth study magnifies these issues. Because the goal of investigation involves the pattern of increments between data points, there is a critical need to pay attention to the effects that an error at one time has on the immediately adjacent points. Formally, this is known as an issue inherent to dependent, negatively correlated data.[40] An example of the magnitude of this problem would be the following: Imagine we have taken a measurement in such a way that we have erred resulting in a "too long" measurement. At the next measurement time, we err in such a way that we underestimate the actual length, resulting in a "too short" measurement. The difference between the two sequential measurements may be negligible, appearing that no growth occurred. In reality, this was an artifact of the combined errors at each measurement. Serial time-intensive data must always be analyzed by a statistical method that takes this possibility into its error assessment consideration.[35]

In our saltatory growth studies, pilot studies are always undertaken to ascertain the measurement error levels with the instrument and sample to be studied.[38] It is best if an independent study of replicate measurement reliability for all parameters to be measured is conducted, and independent intra- and inter-rater measurement error ranges established. A pilot study of time-intensive serial measurements is also conducted. In the initial saltatory studies, the observation window of daily assessment was chosen after it was ascertained that technical errors of measurement were exceeded by measurement increments at the 95% confidence interval. Subsequently, careful documentation of intra- and inter-rater reliability was established in the actual longitudinal studies.[35]

Data analysis

A time intensive longitudinal study produces a time series data set. Traditional time series methods presented in many popular statistical packages for the computer may not, however, be the best approach to growth data analysis. Several issues intervene, the most significant of which is that many of these analytical methods are based on assumptions regarding patterns in the timing of events. These assumptions are likely not to be valid for

biological data and may impose artifactual patterns, such as those resulting from Fourier time series analysis, to be discussed below.

A simple and direct method for time intensive data analysis is to begin with an approach that is designed to ask, where in a data series are significant differences between sequential measurements? With these identified, the occurrence of increments can be investigated for their own characteristics (duration and amplitude) and the intervals between these can be investigated for time duration, trends and random error components. This approach makes no assumptions about the presence or characteristics of increments, or the time between them. The critical aspect of time-intensive data analysis is the identification of actual growth increments from error components in the serial data. This is essential if the goal of the research is to describe the biological nature of the growth process, or the time course and pattern of changes in size. If this step is omitted from an analysis, the results confound error and growth and may erroneously describe error components as biological growth pattern.[41]

Research has shown that each individual's growth trajectory is unique in terms of the timing and amount of growth at saltation events (Fig. 18.3). Therefore, in our studies, we analyze each individual's data separately because a group analysis would obscure saltatory growth as times of saltation and stasis overlap between children (they do not occur with the same amplitude or timing). For an *incremental analysis* of individual data, the t-statistic for serially correlated data is applied to the sequential data.[35] This is an approach that has been used to identify significant differences in time series endocrinological data.

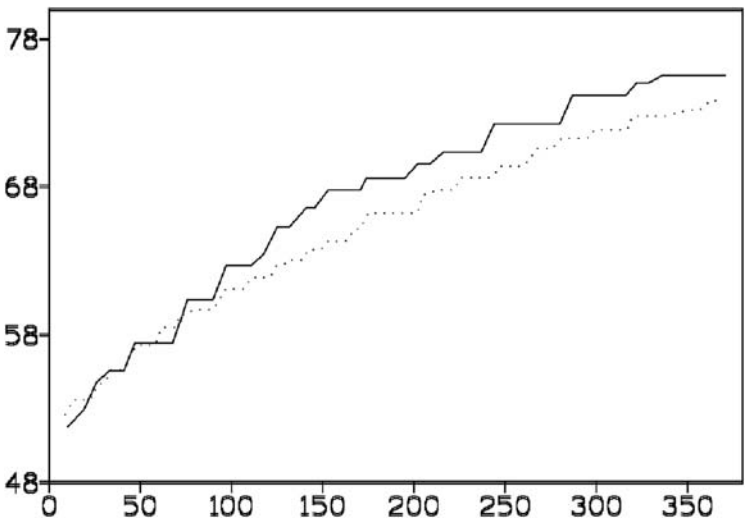


Fig. 18.3

The saltation and stasis patterns for growth in length of two infants during their first year of life. Data were collected according to a University of Pennsylvania human subjects approved protocol.

This statistic identifies significant differences between sequential measurements only when those differences exceed an *a priori* level. We use a 95% confidence limit and the t-statistic cut-off point is calculated employing the individuals' pooled measurement variance, reflecting the significant individual variability in measurement error and the sample size of measurements.[38] This approach accounts for the negatively dependent nature of serial data,[40] makes no assumptions about the underlying temporal process of growth and is relatively robust to non-normal data.[41] Thus, increments that are greater than this calculated value have a probability of about one in twenty that they represent random chance rather than significant change. The t-statistic for stricter levels of significance can also be employed, by altering the t-statistic value used.

This analysis permits the identification of statistically significant sequential positive and negative differences. Significant decreases that accompany significant increases are pairwise investigated for their correspondence to random error components and the remaining differences are further considered. This approach aims to focus the analysis only on sequences in the data where the measurement method identifies significant change and aims to eliminate the description of error components as part of the biology of the growth process.

In our original infant length data analysis, growth increments were identified to punctuate serial measurements during which no significant changes were documented[35]. These observations led to the hypothesis that these intervals represented times during which either growth was unresolvable from error by measurement techniques, or no incremental changes actually occurred. These alternatives were tested in this sample by a comparison of the total growth accrued by each individual during the study (size at the end of the study minus size at the beginning of the study) and the sum of the unique statistically significant growth increments found for each individual. If the stasis intervals were free of incremental growth, the two sums should be equal within measurement error, as the total growth of the child would be accounted for in the sum of the unique saltations. In this study, the total growth of the infants during their study was accounted for in the sum of discrete growth saltations. This analysis was the basis for the formal saltation and stasis hypothesis.[35]

Thus, one initial strategy for analyzing time intensive measurements is to employ a method that asks, can significant growth changes in the data be identified from measurement error? Methods for the analysis of saltatory growth must be based on discriminatory analytical methods that aim to identify significant change from error.[35] It should be noted that data collection methods involving high error and children growing by low amplitude increments have a lower likelihood of saltatory growth resolvability. This does not mean the subjects do not grow by saltation and stasis; it simply means that their growth pattern is not resolvable by the methods employed.

The description of saltation and stasis outlined above generated a hypothesis, or proposition about the underlying biology that is responsible for growth, based on an incremental analysis of serial infant length data and the resulting pattern of growth increments. This observation suggested that growth is a highly controlled event, not a continuous hourly and daily biological signal. The biological hypothesis generated by this observation is that growth is a two-phase process consisting of both a growth suppressive phase (stasis), controlled by growth inhibition, and a discrete growth phase (saltations) that occurs episodically due to either disinhibitory, permissive and/or activation controls. This hypothesis broadly reflects the pattern of growth and dormancy found in nature,[18–23] was in line with what has been observed to characterize cell division and differentiation[13,14] and has strong support as a developmental process whose precise proximate controls remained to be elucidated.[29,31]

Mathematical modeling

The next step in the derivation of the saltation and stasis model of growth involved mathematical modeling. This saltation and stasis model of growth biology can be visualized as a discontinuous staircase model, with both different rises and tread depths between steps. A stepwise mathematical function, flexible in the amplitude and duration of the steps, would be a good approximation of such a biological process and would permit a statistical comparison between saltatory growth and other growth models to be computed.

The saltation and stasis mathematical model was developed by Michael Johnson, a biomathematician who had been working on similar problems in other biological systems.[41,42] The Johnson saltation and stasis mathematical model employs a pulse identification approach that is assumption-free about both how much growth occurs at a saltation and the timing between saltations. It explicitly tests the hypothesis of no growth between the events, and identifies significant growth from error as defined by a probability level based on empirically-determined measurement errors.[35,38]

A mathematical model is a critical step in analysis. Mathematical models are a powerful tool for testing competing hypotheses of biological models.[41,42] Mathematical models provide a statistically-based description of how well a temporal pattern fits an entire data set, and permit statistically-based comparisons between competing patterns. Thus, the researcher can ask, does a saltation and stasis pattern really describe the data better than a model of continuous daily growth? Or, is the saltatory growth notion some sort of artifact from errors in an incremental analysis? Alternatively, are there really stasis intervals between discrete growth changes, or do the growth events take longer than 24 h with some small growth continuing between each event? These questions are statements about entirely different views of the biological process of growth. These viewpoints can be directly compared and a statistical statement of which one best describes the serial growth

data of individuals can be objectively derived. The comparative approach involves applying a mathematical function that represents each of these conceptual patterns to the raw data. The "best fit" of the patterns to the observational data is identified by a comparison of the statistical properties of the residuals, or differences between the fitted function and the experimental data points.[41,42]

For example, in the infant length data, the new saltatory growth model could be compared with the traditional assumptions of continuous growth by fitting a simple curvilinear function through all of the data points. This curvilinear model explicitly models the hypothesis that growth is a continuous daily process. The application of such a function to the raw data in Fig. 18.1 results in a number of data points that are not on the mathematical line (Fig. 18.4). These are residuals, and here they occur in a non-random, wavelike pattern about the line. This illustrates that the line representing the concept of continuous daily growth is not capturing a pattern that exists in the experimental data. The pattern of the residuals suggests that a stepwise or wavelike function is being overlooked by this application, and the "best fit" is the saltatory, not the continuous mathematical function.

A second proposition, that growth is continuous but characterized by growth rate changes, or spurts that take more than one day to complete, is tested by fitting polynomial functions to the serial experimental data. The residuals of this application are likewise investigated for their pattern and magnitude. If a mathematical descriptor fits a data set well, the residuals should be randomly distributed about the resulting model, as expected for random error, and the best-fitting pattern will result in the smallest nonrandom error in the residuals. In our studies, statistical comparisons of the stepwise saltation and stasis

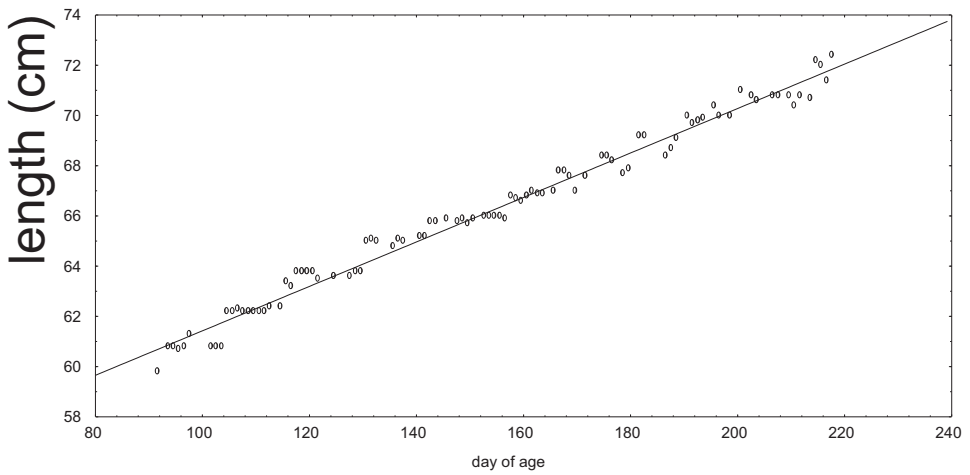


Fig. 18.4

The data set for the infant in Fig. 18.1 with a best fit linear approximation. Note the pattern of data on either side of the line: a nonrandom residual pattern.

mathematical model (a discontinuous function) were compared to polynomial models (functions that characterized continuous growth) (Fig. 18.5) and were found to be better fits of the experimental data than the polynomial models ($p < 0.001$).[32,42]

As shown in these examples, the saltation and stasis model is characterized by smaller and more random residuals by comparison with either of the continuous growth model alternatives. This type of analysis can only establish "best fit" between alternative models and does not exclude the possibility that other, untested models might not be equally good descriptions of the pattern of growth in these data. The analysis does identify that saltation and stasis better describes the data than models of continuous daily growth or a pattern of small and continuous "mini growth spurts".[43]

In summary, mathematical models are fundamental tools for investigating propositions regarding patterns in human growth data and are essential for comparing alternative hypotheses about the nature of the process and underlying mechanisms. To the extent that a mathematical model is a good description of the data, the raw data fit the pattern closely. Raw data that do not fit onto the pattern captured by an equation are the residuals. The better the model as a description of the data, the smaller are the residuals. A well-fit model will have few residuals and those will represent random error as statistically-defined. By fitting a variety of mathematical models to a serial data set, the researcher can objectively test alternative biological models of an underlying growth mechanism.

A number of non hypothesis-driven methods have also been applied to the same data to investigate alternative approaches for the identification of saltatory growth. Details of the methodological considerations established in these studies can be found elsewhere.[44–47]

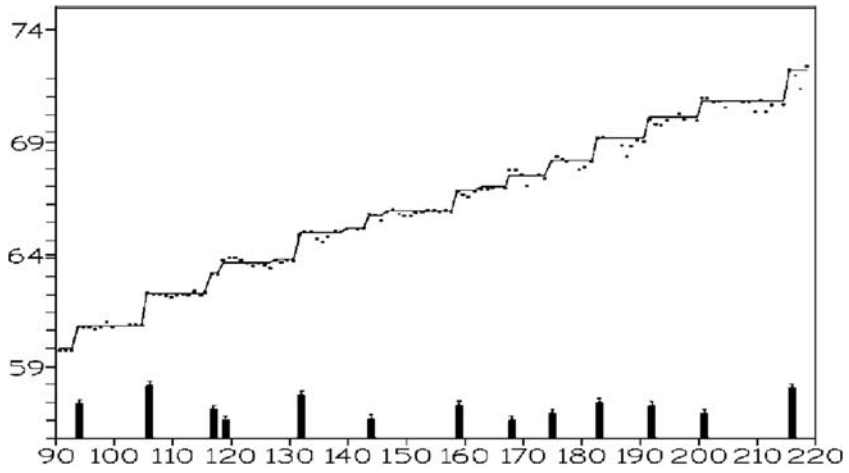


Fig. 18.5

The saltation and stasis mathematical model fit to the data from the infant in Fig. 18.1 with the statistically significant saltations shown below.

Saltatory growth timing

An important scientific issue involves answering the question, "what predicts growth timing?" The short answer is that this is not yet known. Seeking to identify the nature of the temporal characteristics of saltatory growth[31] has involved several approaches to date. Fourier time series analysis of serial growth data permitted investigation of whether saltations occur after regularly spaced time intervals, which would reflect an underlying oscillatory mechanism of constant frequency. The analysis identified that saltations are non-periodic in occurrence.[47]

To investigate whether, by contrast, saltations occur randomly, two methods were employed. First, the observed stasis interval durations were compared to the binomial approximation for random intervals. The experimental stasis interval durations were found to be non-random. Second, Monte Carlo simulations of 1000 randomly spaced saltation events were compared with the observed stasis interval distributions in the data. The experimental stasis interval durations were identified as non-random.[31]

These analyses led to the question, if a biological system is neither predictable nor random, what sort of system is it? We posit that growth proceeds according to nonlinear dynamical principles and is episodically irregular.[31,32] Such systems are typically found in complex, multinodally controlled networks,[48] and advance this as the most likely description of the biological process of growth.[31]

As illustrated here, methods to identify the specific features of saltatory growth timing must be both assumption-free about the nature of the time interval between events and free of imposing artifactual temporal patterns to the data. In the first category are Fourier time series analyses. They are a poor approach to saltatory growth data analysis because they assume that the data series under study exhibits periodic signaling (equal stasis intervals). This method imposes such a conformation on the data whether or not it is extant in the original data series.[43,47,49] Many complex irregular temporal patterns will be resolved by such a program to be periodic, as the method attempts to characterize the unknown serial configurations as cyclical waves. As such, artifactual patterns emerge and the output of such an analysis does not necessarily accurately characterize the original data set. The researcher is left to compare the Fourier analysis results with those of other analytic methods to decide if the periodicities identified are meaningful.

In the second category, or approaches that impose artifactual patterns on data, are smoothing methods and moving average techniques. These approaches alter the temporal characteristics of the original data series and are inappropriate approaches for the identification of saltation and stasis biology because of the patterns that they induce.[49] These methods are particularly inappropriate for data series characterized by short time interval changes as they attenuate, or filter, high frequency information, an effect that

emerges from altering the original data series prior to analysis. The raw data are subjected to a moving average replacement regime: a select number of sequential measurements are averaged and the derived mean becomes the data point in the middle of this interval, replacing the actual measured values. This is repeated for the entire series until a new time series data set is created that consists of a series of interval averages, moving through the data set (hence the nomenclature moving average approach). In this way, a new data series is created that becomes the focus of analysis. Sometimes these approaches are used to decrease the influence of measurement error. This is not the best approach to error consideration in a saltatory growth analysis, or other digital systems. Specifically, if a stepwise function is the actual pattern in the data, a moving average approach will create a slowly changing function and obscure the pattern of both saltation and stasis. This is particularly problematic when data collection occurs with errors of measurement that are equal to or greater than the growth saltations. Analytical smoothing results in the loss of distinctive saltation and stasis characteristics leaving the impression of a continuous pattern. This does not mean that a continuous function is present, only that one is unable to identify the temporal structure with sufficient precision to rule it out, and/or to clarify a saltatory structure.[50] In sum, serial data analyzed by this method are subject to artifactual time characteristics of short-term changes. This will result in the loss of the very specific timing that represents the biology of growth.

Best practices

In summary, research aiming to investigate saltatory growth at the individual level requires attention to details in terms of data collection timing and precision, measurement error assessment, and analytic approach to avoid loss or distortion of biological signal and permit identification of growth saltation timing. Specific care must be taken when measurement error is near or greater than the saltatory increment, which would then be unresolvable, and to include all of the original raw measurement data without imparting any alterations or temporal characteristics. Analysis needs to be undertaken with methods that are assumption-free regarding timing characteristics. Finally, the identification of growth patterns should be amenable to mathematical modeling, and statistical comparisons between growth models is an important investigative step.

The biology of saltatory growth: the model and the evidence

The model of saltation and stasis growth has been investigated at other ages and on other body elements, by alternative methods and on a range of samples and animal systems.

From a developmental age perspective, fetal ultrasound measurements taken thrice weekly document intervals of stasis in fetal body parameters[28] and the protocol of daily

measurements described here has been applied to height during childhood and adolescence with similar results[32] to those from infancy. Regarding other body dimensions, a similar saltation and stasis pattern has been identified in daily measurements of head circumference.[30] Weight, while likely the most frequent measurement in growth studies, is a poor growth estimate as it is primarily a reflection of energy balance. Weekly weight gain patterns did predict subsequent and concurrent length saltations among a healthy sample of predominantly breastfed babies.[51]

Daily measurements on the lower leg of human infants and children, collected by knemometric methods and analyzed by moving average approaches, techniques not designed to identify saltatory growth, find what has been called "mini growth spurts,"[43] as would be expected by moving average analysis applied to a saltatory process.[49] Inspection of published graphs and the authors' conclusions identify that the data series contain stasis intervals and times of growth.

Animal studies include daily measures of both rats' and rabbits' legs using high precision calipers. Among rabbits measured daily, the pattern of lower leg growth appears linear,[52] much like the results of monthly human measurements.[36] Rabbits measured at 3-h intervals,[26] by contrast, show patterns of growth that are compatible with saltatory growth.[29,36] These data clarify that the daily time frame may have no biological relevance, it was simply the smallest time frame for data collection on the infants in the original study. "Daily growth" does not signify an incremental change that took a day to complete, merely the time frame between measurements. It is likely that among smaller animals whose maturational rates are some 100-fold faster than humans, the expression of a developmental growth program may include shorter stasis interval durations and high frequency saltations.

Our best mechanistic understanding of the saltation and stasis model at this time is embodied by cellular activities at the endochondral growth plate, the site of long bone elongation and source of the greater proportion of growth in body length/height. Longitudinal study of growing lambs assessed by a continuous implant telemetry across the growth plate identified expansion events on the order of minutes.[24]

Cell biology studies have specifically identified that these bone elongation events reflect rapid cellular expansion among specialized bone-growth cells at growth plates, known as chondrocytes.[53] These cells effect a *hydraulic "lift" as* a group of cells volumetrically expand, forming a scaffolding structure upon which protein is laid down and mineralization follows.[54] Thus, saltations occur as a coordinated expansion of chondrocytic cells.[55]

This coordination is achieved by way of stop and start mechanisms across the life cycle of the bone growth cells, with sequences of turn "off" and turn "on" chemical mechanisms

orchestrating bone elongation.[56] These sequences include the initial recruitment of stem cells to the chondrocyte lineage, their clonal expansion into functional units that experience orchestrated protein secretory phases, with products that regulate their own arrest or progress, to realize a phase of coordinated transition through volumetric hypertrophy. It is the hypertrophic phase that underlies growing.[53] Waves of chondrocytes emerge together and pass through these steps in tandem. In this way, bones elongate in unique bursts. Modulations in protein synthetic activities both inhibit and promote each step in cell proliferation, migration, differentiation, morphological change, and apoptosis, as multiple networks integrate signals of energy and building block adequacy and act to inhibit or permit passage to the next phase. Clarifying the cascade of biological signals controlling events at each of these critical junctures provides perspective on the mechanisms by which human height variability unfolds as an amalgamation of genetic and environmental inputs. Examples of specific influences at each gated step illustrate the multiple potential paths by which environmental effects interact with genes. Whether through epigenetic pathways or other influences on transcription, translation, post-translational modifications or subsequent protein functionality, many external and local micro-environmental elements can influence height outcome.[56] This occurs as cells at each developmental stage express genes for proteins in support of phase-specific activities as well as proteins that participate in signal reception and transduction in support of cell phase changes.[56,57]

The importance of energy and anabolic resources is emphasized at each of the phases just outlined. While theoretical models positing ontogenetic growth as an outcome of energy and material transformation linked to cellular metabolic reactions have been debated, few of these have considered growth dynamics as contributory.[58] The impact that the biology of saltatory growth may have on these theoretical views is absent, grounded as they are by assumptions of continuous growth. As this is not the biology of growing, it will be important to follow the implications of the saltation and stasis growth model for both broad theory and day-to-day nutritional needs of growing children.

Mechanisms of whole-body saltatory growth patterns remain to be clarified. Biochemical and hormonal studies employing noninvasive investigative techniques in humans suggest that this may an important avenue for investigation.[59] Biochemical approaches for following bone growth in urinary excretions[60] and methods for noninvasive collection of biological specimens among infants show promise.[61]

Saltation and stasis: an integrated model of growth

As parents observe, children grow significantly in short time frames with effects that may be expressed as a lived experienced event for the individual child. Growth saltations are accompanied by changes in behavior: agitation, sleep and appetite perturbations co-occur with growth saltations more than can be explained by chance alone.[62] These observations

suggest that the process of growing may reverberate across physiology. This may reflect side effects of growth biology and/or the operation of a maturational program in which an interaction between cell intrinsic information (genes uniquely expressed in individual cell lines),[63] environmental influences with epigenetic effects,[64] and central neural signals mediated by endocrine, paracrine and cytokine cascades[65] are a network.

For example, it is known that growth in the nervous system and bone occurs by cells that express genes according to a pattern determined by intrinsic programs and external cues.[66–69] Coordinated organismic growth, from a single cell to a three-dimensional form, reflects the expression of proteins transcribed according to a developmental timing intrinsic to cells of similar lineage, determined during embryogenesis, that is modifiable by external input during development.[64–69] From this viewpoint, external input includes metabolic signals transmitted to locally active hormones and cytokines, more directly involved in cellular proliferation and differentiation.

Certainly, a clear understanding of how children grow is important for understanding the process of development in general. Parents, confronted by the behavioral changes that accompany growth, may be better able to assist their children through these episodic growth saltations if they understand the nature of the events.[70]

Much work remains to be undertaken to define the biology underlying the normal process of human growth. Whether saltation and stasis will turn out to be the most accurate description of growth at the cellular, mechanistic level remains to be determined. It is a useful model with which to initiate study into the biology of individual growth and provides a strong theoretical framework with which to conceptualize growth from the level of the cell to the whole organism. The variability in saltation amplitude and frequency provides for substantial variability in growth rate and size, in line with human variation documented worldwide. As the process that takes one cell to a reproductive member of the species, growth that unfolds according to a flexible system responding to multiple inputs with robust adjustments would provide a strategic advantage. Saltatory growth permits multiple paths to final size, moderating maturation and size in a dynamic and interactive system.

Summary

This chapter considered alternative biological models of human growth and reviewed the nature of the empirical evidence for saltation and stasis as the fundamental growth process by which individuals grow. The empirical challenges involved in documenting saltatory growth involve methodological rigor in both data collection (sampling frequency and attention to the measurement errors associated with equipment, observer error and subject) and data analysis, emphasizing the importance of using data analytic methods that do not

impute timing characteristics, but reveal patterns inherent in the empirical data. Best practices specifically caution against the use of smoothing procedures and mathematical models with continuous function assumptions. Insufficient frequency of measurement, inadequate precision in measuring, and inappropriate analytics that limit discrete pulse identification and stasis resolution cannot exclude saltatory growth biology.

Variability in saltation amplitude and frequency patterns characterize individual growth and forms the basis by which both individual phenotypic variability is achieved and developmental age-related growth rate changes occur. Individual growth is personalized. Mathematically modeled statistical predictions of growth trajectories based on averaged individual-level data and population-level growth charts are not resolvable into actual patterns of individual's growing.[71]

The saltation and stasis model is supported by evidence from animal studies identifying saltatory growth at the level of the endochondral growth plate. Cell-level studies document proximal pathways that influence both saltation occurrence and stasis durations from on/off controls at serial hubs. Growth models based on continuous daily growing and either/or partitioning into genes and environment are not in line with growth biology emerging at the cellular level. Instead, growth appears to express systems' networking influences that are managed at hubs and translated through nodal integration and transcriptional controls. This results in managing inhibition/disinhibition mechanisms that emerge as pulsatile cellular events permitting adaptive matching between a developing organism and the environment. This is a fundamentally robust system permitting a wide variety of growth patterns by which to traverse the journey from one cell to adulthood with maximal flexibility.[72]

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CHAPTER 19

Body composition during growth and development

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Introduction

The body is comprised of water, lipids, protein and minerals. The absolute amounts and relative proportions of these compounds change throughout the life cycle. Growth, maturation, and aging, as well as other factors such as disease, nutrition and behavior alter the chemical composition of the body. This chapter will review methods of assessing body composition, the changes in body composition associated with growth and maturation, the role of body composition in determining nutritional needs, and the importance of body composition in human health and disease.

Basic concepts

Chemical maturation and the life cycle

The proliferation, differentiation, expansion, and replacement of cells from conception onward result in changes in the relative and absolute amounts of chemical compounds in the body. For example, at birth, the brain and other organs comprise a large proportion of both lean and total body mass. As the infant grows, the skeletal muscle compartment expands. Although the brain and other organ tissues continue to grow, they gradually come to represent proportionately less of the lean and total body mass. Similarly, at birth, many bones are present as ossification centers and are gradually filled in with bone matrix of hydroxyapatite. During pregnancy, lactation and senescence, bone mass fluctuates and declines. Bone is the major reservoir of calcium in the body. Thus, the calcium content of the body shifts as the body matures and ages. These examples illustrate the process of chemical maturation and how the composition of the body changes during the life cycle.

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Body composition models

The body is formed of basic elements such as carbon, oxygen and hydrogen, which combine into molecules (e.g., water, lipids, protein), tissue compartments (e.g., fat, muscle, bone) and the whole organism.[1] These levels of biological complexity provide a conceptual framework for addressing body composition questions and selecting appropriate methods. For example, to study changes in bone mass during growth and development, an anthropometric measure such as height provides a general measure of the amount of bone for the ***whole organism***. Measurement of bone mineral content by a technique such as dual energy x-ray absorptiometry (DXA) would provide an excellent measure of the size of the ***tissue compartment***. Since the bone is the primary reservoir for calcium, total body calcium (***elemental compartment***) can also be estimated from total body bone mineral content based on the chemical composition of hydroxyapatite (calcium = 0.34 × bone mineral content).[2] This conceptual framework for body composition using levels of biological hierarchy is particularly useful in understanding the assumptions that underlie body composition methods and for defining the limitations of current knowledge of body composition in the life cycle. Infants and children present special challenges in measuring various compartments safely, accurately and reliably *in vivo*.

Many of the methods used to measure body composition are described below. The most commonly used methods partition the body into two compartments (fat-free mass or fat mass). Some newer methods use three (lean body mass, fat mass or bone mass) or four (water, protein, fat, mineral) compartments. Although fat-free mass and lean body mass often are used interchangeably, fat-free mass consists of body weight minus the ether-extractable lipid fraction of the body (fat mass), whereas lean body mass also contains a small amount of essential lipid (2%−3%). Bone mineral is part of the fat-free mass compartment. DXA techniques of bone densitometry (described below) allow for separate assessment of bone mineral mass from lean and fat tissue. Advanced imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) offer new possibilities for understanding, for example, the size and composition of organ and tissue compartments.

Nutrition, adaptation and functional outcomes

The chemical changes in the body during growth depend on the availability of nutrient substrate. Essential nutrients in adequate quantities are required to assure that genetically programmed cell growth, proliferation and differentiation proceeds unhindered. Furthermore, the relationship between body composition and nutrition is synergistic in that nutrient requirements are determined, in part, by the composition of the body. For example, lean body mass (mainly the smooth and skeletal muscle compartments) is the most metabolically active part of the body and is the primary determinant of energy

requirements in normal individuals. With a deficit in energy intake, both fat and lean body mass are used as fuel. The resulting weight loss is composed of losses in both these tissue compartments, thereby altering the energy required for weight maintenance. In growing children, inadequate energy intake may manifest as growth faltering and failure to achieve age-appropriate increases in lean and fat mass, rather than weight loss.

Body composition is also sensitive to behavioral patterns in a similarly synergistic manner. For example, physical activity promotes development and growth of muscle and bones, and prolonged inactivity results in muscle wasting and bone loss. Likewise, physical activity and endurance may be limited by inadequate muscle development. Thus, body composition both reflects and contributes to human adaptation to lifestyles, activity and work patterns, and the social and physical environment.

Tempo of growth

As a child ages and sexual maturity approaches, the hormonal changes associated with puberty produce rapid changes in body composition. Body composition, especially in late childhood and adolescence, is regulated by a "biological clock" rather than chronological time. Children of similar age may be very different in terms of their physical maturation. Similarly, children of the same body size (stature or weight) may be of different ages or stages of maturation due to the biological clock or "tempo of growth." Variability in body composition, between and within populations, may be mediated by differences in the tempo of growth.

Fatness versus fat patterning

Adipose tissue is an important body component for survival. It serves as a reservoir for energy during periods of nutritional deprivation, and it insulates the body from the environment to maintain thermal homeostasis. Excess adipose tissue, or obesity, is associated with a cascade of physiologic abnormalities that can threaten health and well-being. A further consideration is the distribution of fat, or fat patterning. At the whole body level, fat patterns are characterized as "android", with a large amount of fat accumulation on the trunk versus a "gynoid" distribution with greater amounts of fat on the hips and extremities. Fat depots in the abdominal cavity, or in tissues such as the liver or muscle cells are associated with metabolic abnormalities and represent increased risk of health complications independent of the actual amount of excess fat.

Heredity versus environment

Measures of body size, such as height, weight and body mass index (BMI) have a strong genetic component. For example, a recent genome-wide association study identified 3290

single nucleotide polymorphisms (SNPs) associated with height and 941 SNPs associated with BMI.[3] A similar study identified numerous SNPs associated with more specific measures of body composition, such as percent body fat (77 SNPs) and fat-free mass (174 NSPs).[4] However, many of these loci represent noncoding variants, not causal genes, but may eventually provide clues to genetic susceptibility to obesity, such as regulation of energy expenditure.[5] Interestingly, twin studies show that the heritability of BMI varies with age; it is lower in infancy and then increases to about 0.7−0.8 in late childhood and adolescence, and then declines with age as environmental influence have an increasing impact on BMI.[6] The role of the environment in the development of excess adiposity is evidenced by the increasing rate of obesity in the US[7] and globally.[8]

Methods

The techniques used to assess body composition are an important part of the field itself, because of the shortcomings and limitations of all methods. With the exception of cadaveric studies, nearly all other body composition methods are indirect and involve assumptions that may introduce a bias in the results. Therefore, each method needs to be evaluated in the context of the quality of information obtained, the level of expense and risk involved, and the biological issue of interest for any given research study or clinical investigation.

Anthropometry

With measurements obtained by a well-trained anthropometrist, anthropometry under many circumstances can be a highly suitable method for body composition assessment in population based studies or screening tool for disease risk. The tools are moderately simple, precise, portable and inexpensive, and the anthropometric exam is rapid and non-invasive. The tools used for anthropometric evaluations include scales, stadiometers, anthropometers, tape measures and skinfold calipers. Weight and length or stature, the most basic information used to assess growth and nutritional status, are also used to form indices that provide an approximate representation of body composition.

The most commonly used index is the BMI, calculated as weight (kg)/stature $(m)^2$. To screen for overweight and obesity, BMI growth charts are available from the US Centers for Disease Control and Prevention,[9] the International Obesity Task Force,[10] and from the WHO Multicenter Growth Study[11] for infants and young children. In infants, weight for length is commonly used, but for very young infants, BMI is a better indicator of body composition[12] and predictor of later adiposity.[13] BMI is useful as a screening tool for both excess adiposity and undernutrition, although it has several drawbacks. During adolescence, BMI is influenced by the timing of puberty and may poorly represent

adiposity. In addition, a high BMI may be due to high lean body mass and normal adiposity, and normal BMI can occur with stunting and low lean mass. The relationship between BMI and adiposity varies between populations; in particular, South Asians have a higher percent body fat and more visceral fat at a given BMI than people from other geographic locations.[14,15] For undernutrition, lean mass performs better in predicting health outcomes, such as length of hospitalization and medical complications, than BMI.[16]

Upper arm anthropometry is also widely used as an indicator of the composition of the whole body. Mid-upper arm circumference and triceps skinfold thickness measures are used to compute the total area, fat area, muscle area, and muscle circumference of the upper arm (Table 19.1).[17] At the population level, these measures correlate well with whole body measures of body fatness and muscularity even though they are measured at a single site. In addition, there are reference data available for these derived measures,[18] so that it is possible to assign a percentile rank or standard deviation score to an individual's measure which indicates whether that person is relatively muscular or fat in comparison to same age-and-sex peers.

Waist circumference is a simple anthropometric measure that is a good indicator of both overall body fat and fat distribution, particularly when expressed relative to stature as the waist to height ratio. The waist-to-height ratio, usually at a cut-off of approximately 0.50, identifies children with cardiometabolic complications but offers only marginal improvement over BMI.[19] It is important to note that the measurement technique for waist circumference is poorly standardized, making it difficult to compare across studies and establish reference ranges.[20] At least one study demonstrated that the waist circumference measurement techniques vary in their association with metabolic syndrome in adolescents.[21]

Anthropometric measures can also be used to estimate whole body fat-free mass, fat mass, and percent body fat. This technique is based on prediction equations established from comparisons of skinfold measures with a criterion method such as hydrodensitometry or dual energy x-ray absorptiometry (DXA) (see below). This approach assumes that the prediction equations are generalizable from the samples from which they were derived, and that body density is the same across age and sex groups. Despite these assumptions,

Table 19.1: Formulas for computation of upper arm indicators of body composition.

Upper arm muscle circumference (mm) $= C - \pi T$
Upper arm area (A) (mm^2) $= (\pi/4)\,(C/\pi)^2$
Upper arm muscle area (M) (mm^2) $= ([C - \pi T]^2)/4\pi$
Upper arm fat area (F) (mm^2) $= A - M$

C, upper arm circumference; *T*, triceps skinfold.
Note: check your units, convert arm circumference to mm by multiplying by 10.
From Frisancho A. New norms of upper limb fat and muscle areas for assessment of nutritional status. Am J Clin Nutr. *1981;34:2540–2545.*

the FFM and FM estimates correlate well with independently derived estimates such as DXA, even across groups of children that vary in body habitus.[22] Table 19.2 provides sets of prediction equations that illustrate age, gender and ethnicity specific equations. Anthropometric measures are also used to derive indicators of fat patterning, such as the waist-hip ratio (using waist and hip circumference), or the centripetal fat ratio defined as subscapular skinfold/(triceps + subscapular skinfold), using the triceps and subscapular skinfold measures.

Body breadth measures, such as biacromial, biiliac, elbow and wrist diameters can be informative as part of the anthropometric description of body composition,[23] although they have not been used extensively. Because they quantify frame size, they correlate well with

Table 19.2: Body composition prediction equations for percentage body fat.

	Non-African American	African American
2-Skinfold prediction equations		
Males		
Tanner 1–3	(13.12 × log sum 2SF) − (15.46 × Log height) + 64.58	(14.73 × log sum 2SF) − (10.55 × Log height) + 34.82
Tanner 4–5	(13.12 × log sum 2SF) − (13.27 × Log height) + 50.92	(14.73 × log sum 2SF) − (25.95 × Log height) + 110.54
All[a]	(14.28 × log sum 2SF) − (21.50 × Log height) + 90.69	(14.28 × log sum 2SF) − (19.23 × Log height) + 78.29
Females		
All	(13.95 × log sum 2SF) − (18.09 × Log height) + 77.17	(13.95 × log sum 2SF) − (18.09 × Log height) + 75.40
4-Skinfold prediction equations		
Males		
Tanner 1–3	(12.41 × log sum 4SF) − (16.90 × Log height) + 66.78	(14.68 × log sum 4SF) − (16.90 × Log height) + 58.32
Tanner 4–5	(12.41 × log sum 4SF) − (16.90 × Log height) + 64.94	(14.68 × log sum 4SF) − (16.90 × Log height) + 56.48
All[a]	(12.74 × log sum 4SF) − (21.47 × Log height) + 87.82	(14.83 × log sum 4SF) − (21.47 × Log height) + 79.92
Females		
All	(13.99 × log sum 4SF) − (21.42 × Log height) + 85.65	(13.99 × log sum 4SF) − (14.69 × Log height) + 51.04

Sum 2SF: sum of triceps and subscapular skinfold thicknesses.
Sum 4SF: sum of triceps, biceps, subscapular and suprailiac skinfold thicknesses.
[a]Simplified equation that does not require Tanner Stage.
Adapted from Wendel D, Weber D, Leonard MB, et al. Body composition estimation using skinfolds in children with and without health conditions affecting growth and body composition. Ann Hum Biol. *2017;44:108–120.*

measures such as bone mineral density, or can be used to distinguish between large versus small frame individuals when BMI is being used to characterize adiposity.

Densitometric methods

Densitometric methods are based on the principle that body density can be determined as body mass divided by volume. Body density is then used to estimate fat-free mass, fat mass and percent body fat using conversion formulas. The method is based on several assumptions, including the assumption that the densities of the major tissue compartments (density of fat = 0.900 g/cc and fat free mass = 1.100 g/cc) are essentially constant across individuals. However, these constants vary with growth, maturation, illness, degree of obesity and aging. The Siri and Brozek formulas (Table 19.3) are the most widely used conversion formulas in adults. Lohman[24] and Wells[25] have published age and sex-specific constants for children to be used in equations similar to that of Siri, that take into account the chemical immaturity of the growing child. In children and adolescents, the chemical composition of the body changes, particularly with respect to the decreasing water and increasing mineral content of fat-free mass. For example, the density of fat-free mass in 8 year old boys is 1.088 g/cc and for girls it is 1.090 g/cc[25], as opposed to the value for adults of 1.100 g/cc.

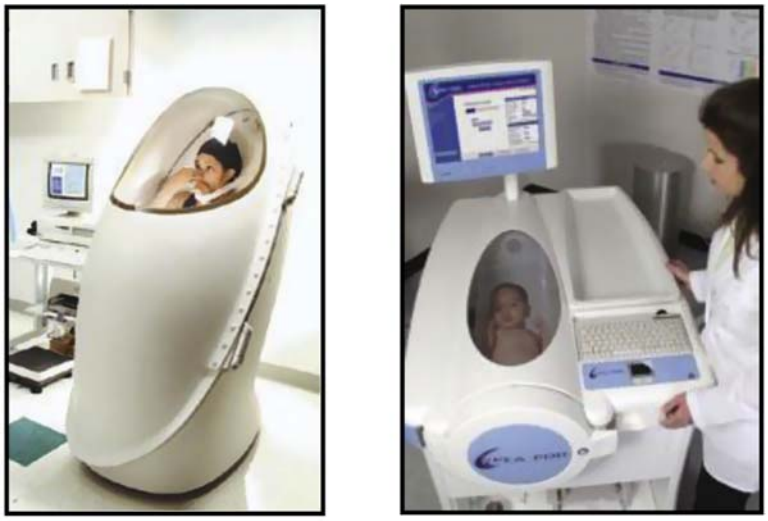
Hydrodensitometry, or underwater weighing, was previously the most readily available criterion method for assessment of body composition (fat-free mass and fat mass). It has been used mainly in adults and adolescents, and can be used in children ($\geq$8 years) who are healthy, ambulatory and have normal cognitive status. Body volume is determined from measurement of body mass in air and while immersed in water using Archimedes' principle. According to Archimedes' principle, the apparent weight of an object immersed in water, relative to its weight in air, is decreased by an amount equal to the weight of the displaced water. One ml of water has a mass almost exactly equal to 1 g. Therefore, the difference between the mass in air and the mass under water (in grams) is equivalent to the volume (in mL) of the object. The density is then calculated as mass divided by volume. Corrections are needed for the volume of air in the lungs and intestines, and for the density of air and water.

Air displacement plethysmography is similar to hydrodensitometry in using mass and volume to measure body density. This method uses the displacement of air to estimate body volume. Fig. 19.1 shows the Bod Pod® (Life Measurement Instruments, Concord, CA)

Table 19.3: Prediction of body fat using body density measurements.

Siri (1956) % body fat = $(4.95/D_b - 4.50) \times 100$
Brozek (1963) % body fat = $(4.570/D_b - 4.142) \times 100$

D_b = body density.



Bod Pod Pea Pod

Fig. 19.1: Air displacement plethysmography (ADP).

ADP measures body density through measurement of body mass and volume. The Bod Pod is a commercially available device for use in children and adults. It requires the subject to be minimally clothed in spandex shorts or bathing suit, with a spandex hair covering, to minimize air trapping around the body. The Pea Pod is designed for infants who are placed in the chamber without clothing or diapers. The measurement time is approximately three to 5 min

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body composition analyzer, for children and adults, and the Pea Pod for infants. Both devices contain a two compartment chamber of known size. Using a pulsating diaphragm between the two chambers to vary the pressure, the displacement of air when a subject is seated in the outer chamber is measured. A breathing apparatus is built into the device to estimate lung volume for a more accurate estimate of body density. Once body density is determined, the calculations are similar to those for hydrodensitometry.

One of the major sources of bias in the densitometric methods involves the assumptions about the water and mineral content of fat-free mass. Multicompartment approaches that include other measures such as total body water (TBW) to measure the water content of the fat-free mass, and dual energy absorptiometry to measure bone mineral content, greatly improve the accuracy of body composition estimates, especially in growing children.[26]

Isotope dilution methods

Stable isotopes are used to estimate the size of various compartments of the body using the classic dilution principle. Provided proper sampling, dosing and storage procedures are

followed, this method is very accurate[27] and measurement error is mainly related to the laboratory analysis of the isotopic concentrations. The stable isotopes, deuterium oxide ($^2H_20$) or oxygen-18 (O^{18}), are naturally occurring isotopes. They are a safe, effective and non-invasive means of measuring the size of the total body water pool (TBW) in infants and children. Because these isotopes are naturally occurring, they are already present in the body and a baseline body fluid sample (such as blood, urine or saliva) must be obtained. Then, a small but concentrated dose of isotope is administered orally which elevates the concentration of the isotopes in the body above that observed from drinking water. After an equilibration period during which the isotope mixes with the total body water pool (usually about 4 h), further sample collections are acquired. Samples are analyzed by mass spectrometry. The rise in isotopic concentrations from baseline to the post-dose equilibrium is proportional to the total amount of water in the body. Due to mixing of the isotopes with non-aqueous fractions of the body, $^2H_20$ overestimates TBW by about four percent, and O^{18} overestimates TBW by about one percent. Fat-free mass is derived from the TBW measurement using hydration factors[25] which estimate the fraction of the total body water in fat free mass. Once fat-free mass is estimated, fat mass and percent body fat can then be derived (fat mass = body weight − fat-free mass; percent body fat = fat mass/body weight × 100).

The compartmentalization of water in the body can also be determined using the isotope dilution method. Bromide and isotopic chloride dilution are used to estimate the extracellular water compartment so that the distribution of the total body water pool into the intra- and extra-cellular water compartments can be determined.

Bioelectrical methods

Bioelectrical impedance analyzers (BIA) use the electrical properties of water and electrolytes in the body to estimate the water, fat-free mass and fat mass compartments of the body. BIAs measure the impedance of a low energy electrical signal as it passes through the body. The body fluid compartment, rich in electrolytes, has the least impedance to the flow of an electrical signal, whereas the lipid and bone compartments have greater impedance. Original devices used source and detector electrodes placed on the hand and foot to measure impedance of the entire body, or at other locations to determine impedance of body segments. Some newer BIA models measure foot-to-foot impedance and appear similar to bathroom scales with metal foot pads for bare feet. Others use hand-to-hand impedance or a combination of hands and feet. In all models, there are assumptions about the shape and distribution of the tissues being measured and calibration equations are needed to convert the resistance signal to estimates of body composition. Resistance, one of the key components of impedance, is disproportionately affected by the resistance in the limbs; arms and legs contribute close to 50% of whole body resistance in some BIA systems, whereas the trunk contributes 5%−12% to whole

body resistance measures.[28] These findings underscore the potential bias that can result from shifts in fluid distribution in the body.

Prediction equations for BIA devices usually require measurement of height and weight. Care should be taken to use the prediction equations devised for children and for the appropriate ethnic group, as ethnic specific equations are required.[29] Differences by disease group, such as cystic fibrosis[30] and weight or nutritional status.[31] Generally, BIA devices are appropriate for characterizing groups of individuals, but do not accurately measure body composition at the individual level compared to reference methods.

Multi-frequency BIA and bioelectrical impedance spectroscopy operate on similar principles. They have the added advantage of using both lower and higher frequencies to estimate the intracellular and extracellular water compartments. At low frequencies (up to 5 kHz), the current is unable to penetrate the cell membrane, so impedance is attributed to the extracellular water compartment. At frequencies of 100−500 kHz, both the intra-and extracellular water compartments impede current flow, so total body water is estimated. Since total body water and extracellular water are estimated in these two ranges, the intracellular water compartment can be derived. Bioelectrical impedance spectroscopy devices sample across the full range of frequencies and use mathematical models to determine water compartments.[28] Generally, they are more accurate than single frequency BIA in predicting water compartments, although the mathematical models used produce variable results.[32]

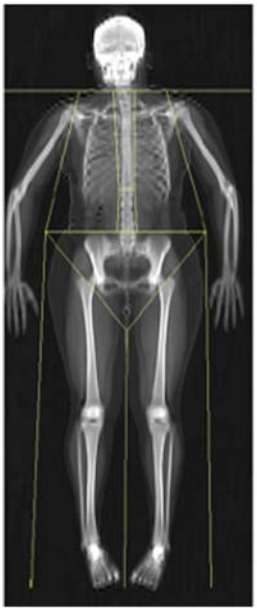
Potassium − 40

Potassium is found mostly in the intracellular fluid, and is used to estimate body cell mass. Body cell mass is the fat-free intracellular space and the most metabolically active part of the body.[33] It consists of the intracellular fluids and a smaller proportion of intracellular solids of the organs and muscles, and excludes extracellular fluids and solids (such as bone mineral and collagen). A constant ratio of intracellular fluid to body cell mass is assumed, so measurement of total body potassium can be used to estimate body cell mass (body cell mass = total body K (mmol) × 0.0083). Potassium (^{40}K) is a naturally occurring stable isotope found in human tissue. ^{40}K emits a strong gamma ray which can be counted in a lead-shielded room (^{40}K counter) with a gamma ray detector for determination of the whole body content of ^{40}K. ^{40}K occurs as a very small percentage of the non-radioactive ^{39}K also present in the body, and total body potassium occurs in the ratio of ^{40}K/0.0118%. Since potassium is within the intracellular space, ^{40}K also can be used in combination with TBW to estimate the intracellular and extracellular fluid compartments of the body.

Absorptiometry methods

The early absorptiometry methods used dual photon absorptiometry (DPA) with a radionuclide source and digital detector to determine body composition. Dual energy

x-ray absorptiometry (DXA), using a low energy x-ray source, is now more widely used because of its greater accuracy. DXA measures three body compartments; bone mass, lean body mass and fat mass. Each of these tissues varies in density, and therefore they attenuate the energy beams differently. DXA involves radiation exposure, although the exposure is extremely low (3.5 mrem). Whole body estimates of body composition for infants, children and adolescents can be obtained in less than 5 min (Fig. 19.2). The image of the body is divided into subregions to quantify the body composition of the limbs and torso separately. This is a distinct advantage of DXA over many other methods. A large proportion of total body lean mass is comprised of organ tissue. Summing the lean mass of the arms and legs, referred to as appendicular lean mass, is a good estimate of skeletal muscle mass. For some purposes, measures of skeletal muscle mass are extremely relevant since it is more responsive to physical activity and nutritional stress. DXA also estimates the composition of the "android" and "gynoid" regions, and visceral adipose tissue at a lower cost and with less radiation than other methods close to the waist.



Body Composition Results

Region	Fat Mass (g)	Lean + BMC (g)	Total Mass (g)	% Fat	%Fat Percentile YN	AM
L Arm	1998	1954	3952	50.6		94
R Arm	1751	2078	3829	45.7		87
Trunk	14687	16207	30894	47.5		97
L Leg	5535	6271	11806	46.9		88
R Leg	5804	6293	12097	48.0		90
Subtotal	29776	32802	62578	47.6		96
Head	1194	3272	4466	26.7		
Total	**30970**	**36074**	**67044**	**46.2**		**95**
Android (A)	2210	2178	4387	50.4		
Gynoid (G)	4948	5468	10416	47.5		

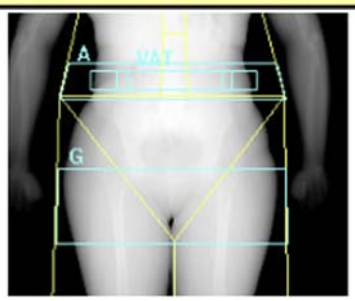


Fig. 19.2: Dual energy X-ray absorptiometry (DXA).

DXA uses the attenuation of X-ray beams to assess body composition. Fat, muscle and bone differ in density, so they attenuate the X-ray beams in varying amounts. (A) shows that fat, muscle and bone of a whole body image in an obese female, and accompanying body composition analysis results for each sub-region of the body. (B) Shows the outline of the android region (A) in the mid-trunk area, the gynoid region (G) in the hip area, and visceral adipose tissue region (VAT) in the center of the body.

For subjects with metal implants, who are not able to lie supine or who are unable to complete a measurement without movement, DXA derived body composition estimates are suspect. However, since variability in bone mineral density is one of the primary sources of error in the estimation of the density of fat free mass, DXA measurements are more accurate in estimating fat free mass than techniques that use a two compartment model such as densitometry. Compared to bioelectrical and anthropometric methods of body composition assessment described above, it has the added advantage of being independent of sample based prediction equations.

Body composition determined by different DXA systems are not interchangeable as there are slight differences in equipment and software design and results between manufacturers.[34] For children, the accuracy of DXA body composition estimates are an even greater concern because changes in hardware and software by the same DXA manufacturer have had a large effect on body composition estimates.[35–37] Few validation studies of DXA body composition have been performed in children. One study compared percent body fat by DXA with percent body fat from the "gold standard" four-compartment model in over 400 healthy children 6–18 years of age.[38] They found that DXA underestimated fatness in subjects with lower percent body fat and overestimated fatness in subjects with higher percent body fat. However, there was a strong relationship between the two measures ($R^2 = 0.85$). In a similar study of obese children, DXA overestimated fat mass and underestimated lean mass.[39] Nevertheless, because DXA is widely available, relatively safe, and precise,[40] it is often the technique of choice in body composition assessment in children.

Neutron activation

In vivo neutron activation analysis is a very specialized method for measuring atomic level components of the body. The major elements are Ca, C, Cl, H, N, Na, O and P, and trace elements of Al, Cd, Cu, Fe, and Si are also measured. There are only a handful of research centers worldwide that use neutron activation analysis and it is not an acceptable technique for infants and children. However, it is extremely accurate and the only *in vivo* method for this kind of body composition assessment. While resting in a shielded chamber, the subject is bombarded with a dose of fast neutrons. The neutrons interact with the nuclei of the element or elements of interest (e.g., carbon or nitrogen), forming unstable isotopes which emit gamma radiation. The whole body gamma radiation counter is then able to determine the total quantity of the element in the body.[41]

Computerized axial tomography

CT scans give three dimensional images for regional analysis of body composition. While whole body analysis is possible, it is quite impractical due to the expense, time, and radiation exposure involved with the technique. CT systems use an x-ray source and

detector, and the attenuation of the x-rays is used to construct the image of the tissue area. Image production can be generated from "slices," or spiral images. CT scans have been used effectively to estimate visceral adipose tissue, organ volumes, the area and density of vertebral bodies, and skeletal muscle mass. Peripheral CT devices are also available for imaging the bone (especially cortical vs. trabecular bone), muscle and fat at appendicular sites such as the distal radius or tibia.[42] Muscle density can also be determined by peripheral CT devices.[43] Fig. 19.3 shows the bone, muscle and fat from a peripheral QCT image obtained at the 66% distal tibia site.

Magnetic resonance methods

Magnetic resonance imaging generates detailed images of organs and tissues using a powerful magnetic field combined with radio frequency pulses that excite the hydrogen atoms in tissues. It has wide application in body composition for purposes such as

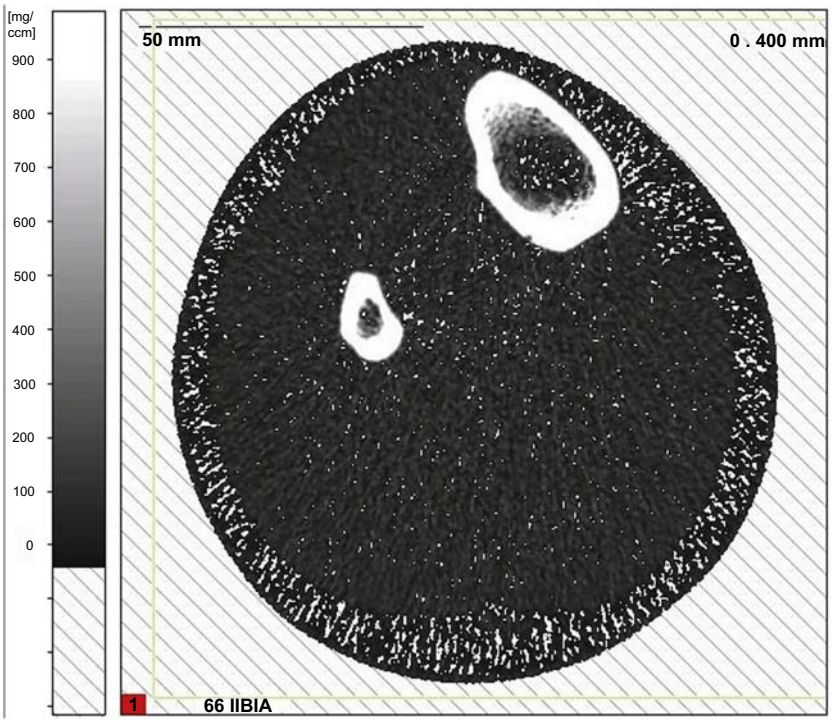


Fig. 19.3: Peripheral quantitative computed tomography (pQCT) image of muscle, subcutaneous fat and bone at the 66% distal tibia.

pQCT is table-top device that is able to measure trabecular bone mineral density at the ends of long bones, and cortical density and dimensions in the mid-shaft of long bones. It is also able to quantify the amount of muscle, fat and bone in specific regions. Shown here is the pQCT image taken at 66% of tibia length in the mid-shaft. It is also the site of maximal muscle circumference.

determining the volume of visceral adipose fat, organ volume, skeletal muscle size, quantification of intermuscular adipose tissue[44] and water content of bone.[45] Quantitative magnetic resonance (QMR) devices can assess total body fat mass, fat-free mass and water. It is a safe and rapid test, so quite feasible for infants and children, but the equipment is not widely available. More recently, nuclear magnetic resonance spectroscopy has been used to measure of intramyocellular and intrahepatic lipid fractions.[46]

Ultrasound methods

Ultrasound methods have been used to estimate fetal weight, dimensions and regional body composition.[47] Postnatally, ultrasound is used to estimate body composition at specific body sites by measuring tissue thicknesses. Most commonly ultrasound is used to assess visceral and subcutaneous fat thickness. It has also been used to quantify muscle cross-sectional area and muscle echogenicity, an indicator of intracellular fat content of muscles.[48] To date, ultrasound methods have not been used frequently in body composition assessment in children.

Body composition and growth

Infancy

Water content of the human fetus is high and is about 75% of body weight at birth. Following birth, there are rapid changes in hydration. During the first few days of life, the term infant loses 5 to 10% of body weight, much of which is water (mainly extracellular). The extracellular water as a percent of body weight declines from 42.5% on the first day of life, to 26% by 10 years of age. Intracellular water increases from 27% to 35% over the same time period.[49] The composition of lean tissue is significantly affected. At birth, the hydration of fat-free mass is approximately 80%, and declines to 78% by three months of age.[50]

Human infants are born with a large head relative to the size of the total body. At birth, the brain represents 13% of total body weight (compared to 2% of total body weight in adulthood). Other organs, e.g., heart, lung, liver, etc., also comprise a large percentage of infant body mass. Thus, organ tissue makes a greater contribution to body weight and lean body mass during infancy.

Infancy is one of the most rapid periods of growth during the human life cycle. Weight and length increase rapidly and birthweight is usually doubled by four to five months of age. During infancy, BMI correlates well with adiposity and is predictive of later obesity.[12] BMI increases rapidly and reaches a peak around 9 months of age and then declines. Infancy peak BMI is greater in boys than girls, and varies according to population

ancestry.[51] Interestingly, the genetic loci associated with infancy peak BMI differ from those associated with adult and child BMI.[52]

With the rapid changes in BMI that occur during infancy, fat and fat-free mass increase. Fat as a percentage of total body weight peaks at about 3–6 months. A comprehensive study of body composition changes in the first year of life showed that by six months of age, average percent body fat for boys was 29.1 ± 4.7, and for girls it was 32.0 ± 4.4%.[53] Boys also had significantly greater fat-free mass, total body water, total body potassium and bone mineral content than girls throughout infancy. Thus, girls and boys differ in body composition, even during infancy. In addition, feeding patterns influenced the changes in the amount and relative proportions of the fat and fat-free mass compartments in these infants; breastfed infants were not as heavy and had less fat at 9 and 15 months of age compared to formula fed babies.[54] However, recent data suggests that differences in growth between breastfed and formula fed babies do not persist into childhood.[55]

One of the unique features of newborns is the greater amount of brown adipose tissue compared to the amount found in children and adults. It is a highly vascularized and enervated tissue, rich in mitochondria, found in the interscapular, supraclavicular, axillary, neck and suprarenal regions of the body. It is highly metabolically active and functions to maintain body temperature. It develops during gestation and its abundance peaks around the time of birth, and begins to decline during infancy. Brown adipose tissue may be an adaptation to the low amount of skeletal muscle in infants which reduces their ability to maintain temperature homeostasis through shivering.[56]

Childhood

During childhood growth proceeds at a far slower pace in comparison to infancy and adolescence. Likewise, growth in body compartments and changes in chemical composition also proceed at an unremarkable pace. During this period, sex differences in body fatness are apparent with girls, on average, having a higher percent body fat than boys even prior to the onset of sexual maturation.

The mid-childhood growth spurt, which occurs in many children around ages 6–8 years, is a small increase in the rate of gain in weight, height and body breadth. At approximately the same age, the body mass "rebound" occurs. BMI peaks near the end of infancy, and declines from early childhood (1 year of age) reaching a nadir at about ages 5–6 years. BMI then begins to increase continuing through adolescence and into adulthood. The "rebound" refers to the turnaround in BMI,[57] the timing of which may be genetically regulated.[58] Children who experience this rebound at an earlier age are more likely to have a higher BMI and become obese, although they are not necessarily obese at the time of rebound.[59] Recent studies suggest that they are also at increased risk of

complications such as type 2 diabetes.[60] The age at adiposity rebound varies by population ancestry and SES.[61]

Adolescence

The onset of sexual maturation is associated with profound and rapid changes in the body compartments and chemical maturation. These changes are primarily due to the effect of gonadal steroids on the tissues (muscle, fat, bones and organs). Although sex differences in body composition are present during infancy and childhood, they become far more pronounced during adolescence.

Adolescent body composition changes are due to the rapid increases in body mass associated with the pubertal growth spurt. Organs such as the heart and brain increase in size during this period. Fat and lean mass change in absolute amount and relative proportion. Girls gain steadily in fat and fat-free mass through childhood, but there are more rapid gains in these compartments and in percent body fat associated with puberty. Growth of breast tissue contributes to the gain in overall fat mass and percent body fat, as does the gradual attainment of a mature female fat distribution with additional fat at the hips and thighs. Many boys experience a pre-pubertal fat spurt. The subsequent adolescent growth spurt in boys results in significant gains in lean body mass, reductions in fat at the extremities (such as at the triceps skinfold site) and increasing fat deposition at the trunk (such as at the subscapular site). Cross-sectional patterns of changes in fat and lean mass associated with age and puberty are shown in Figs. 19.4 and 19.5.

Bone mineralization also changes significantly during adolescence. Approximately 40% of peak bone mass (the maximum amount of bone in the body during one's lifetime) is attained during adolescence.[62,63] During the adolescent growth spurt, the expansion of the skeleton is due to both increasing height and breadth, and the gain in bone and lean mass continues after cessation of height growth (see Fig. 19.6).[64] The density of cortical and trabecular bone compartments also increases during puberty.[65,66]

Adulthood and senescence

Body mass and composition continue to change during adulthood, although generally the changes are not as pronounced as during adolescence or infancy. In most westernized countries, adults continue to gain weight through adulthood. The age-associated increase in BMI is mainly increased fatness. DXA-based body composition results from the US National Health and Nutrition Examination Survey show that percent body fat and fat mass index continue to increase through adulthood in males and females.[67] For example, median percent body fat values for males of European ancestry are 23% at age 20 and 31% at age 70, and for women are 35% at age 20 and 43% at age 70. Median values for

Fig. 19.4: Age-related changes in fat and lean mass by DXA in males and females. Males and females have distinct age-related patterns of growth in lean and fat mass. Data shown are based on a cross-sectional study of over 800 youth in Philadelphia (The Reference Project on Skeletal Development). Lean mass increases rapidly around the ages when the adolescent growth spurt occurs, but males gain considerably greater amounts of lean mass than females. Fat mass increases with age in females throughout childhood and adolescence.

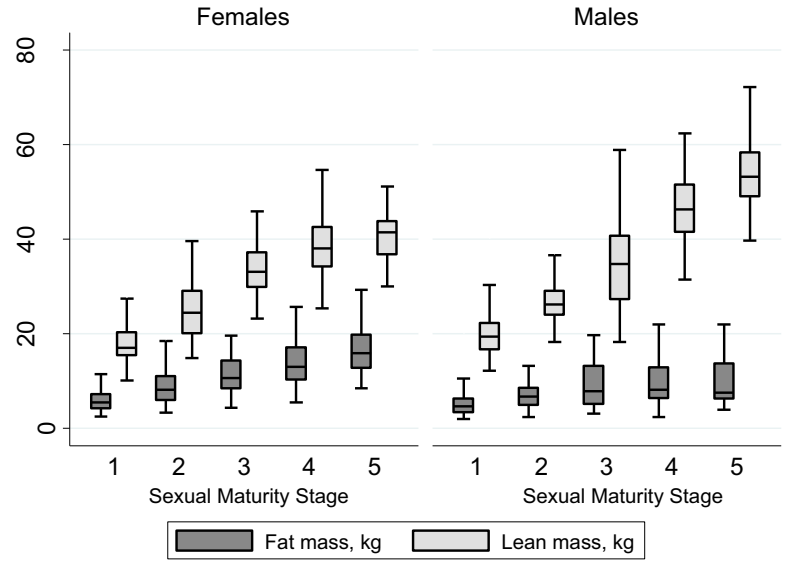


Fig. 19.5: Puberty -related changes in fat mass and lean mass by DXA in males and females. Fat and lean mass increase significantly as puberty advances. Data shown are based on a cross-sectional study of over 800 youth in Philadelphia (The Reference Project on Skeletal Development). Puberty stage was determined by a self-assessment pictograph and questionnaire that described the five stages of breast (girls) and genital (boys) development.

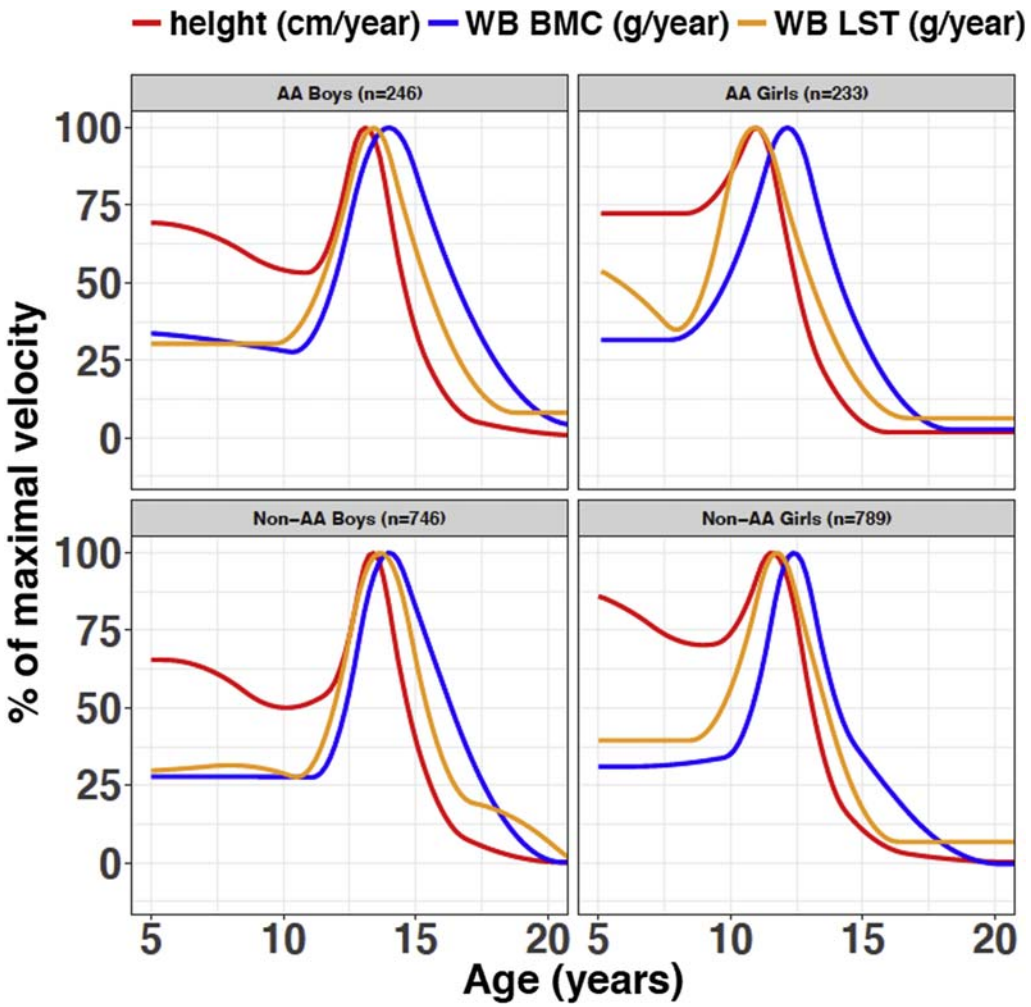


Fig. 19.6: Peak velocity in height, whole body bone mineral content and lean soft.
The adolescent growth spurt is characterized by rapid changes in the size and composition of the body. The spurt occurs earlier in males than females, and there are some differences between populations in timing of the spurt. This figure shows the relationship between the peak and subsequent decline in the rate of accretion in height, whole body bone mineral content (WB BMC), and whole body lean soft tissue (WB LST) in African American (AA) and non-African American (non-AA) males and females in a longitudinal study of healthy children in the US. Note the accrual of bone and lean mass continue after height growth is complete. *Adapted from McCormack SE, Cousminer DL, Chesi A, et al. Association between linear growth and bone accrual in a diverse cohort of children and adolescents.* JAMA Pediatr. *2017;171:e171769.*

lean mass index peak around age 40 to 50 for both males and females and decline thereafter. Traditional non-westernized societies do not experience similar gains in adult weight or BMI, although with increasing modernization, the age-related increases in

weight and BMI mimic westernized countries. Toward the end of life, there is often a loss of body weight, particularly the fat-free mass compartment, that can be due to underlying illness, reduced physical activity, poor nutritional intake and poor nutrient absorption.

In women, changes in reproductive status (pregnancy, lactation and menopause) are associated with rapid and significant shifts in body composition. Fluctuations in bone and fat mass can be particularly pronounced, due to the effect of hormonal changes on these body compartments. During pregnancy, women gain in total body water (4−6 kg) and fat (2−4 kg), in addition to the gains associated with the fetus, placenta and amniotic fluid. Hydration of fat free mass increases from 72.5% at 10 weeks gestation to 74% at term,[68] and water shifts from the intracellular to extracellular compartment. These changes alter some of the assumptions that underlie standard body composition techniques. During the teenage years, the body composition changes associated with pregnancy can include the combined effects of pregnancy and ongoing growth of the mother, simultaneously. For these very young women, pregnancy may have long-lasting effects on body composition in terms of increased adiposity and reduced bone mass.[69] Loss of bone mass and density are associated with pregnancy and lactation, however recovery of bone mass appears to be fairly rapid and complete with the onset of post-partum menses and cessation of lactation.[70]

Menopause is another period of body composition change for women. Overall fatness increases, especially on the trunk and in intra-abdominal fat depots following the mid-life hormonal changes.[71,72] Skeletal changes also occur. In the years just prior to and following the onset of menopause, there is significant bone loss under natural conditions (i.e., without hormone replacement therapy). One longitudinal study estimated a 10% loss of bone density at the lumbar spine region.[73] The loss of trabecular bone, especially of the spine, can be particularly profound.[74] In premenopausal women, the trabecular bone loss has been estimated at −0.45 mg/mL per year; for perimenopausal women it was −4.39 mg/mL per year and postmenopausal women was −1.99 mg/mL per year. These changes can result in osteoporosis, and increased risk of hip fracture with its associated mortality risk. Men also experience declines in lean tissue mass and bone mass, but in a more gradual fashion than women.

Body composition in health and disease

Body composition is influenced by heredity, behavior, health, disease, development and the environment. Body composition patterns in childhood can have lifelong consequences in terms of overall health, physical activity patterns, and work productivity. Several examples of the importance of body composition are described below.

Body composition as an indicator of nutritional status

Body composition assessment is especially important for the information it can provide about nutritional status. In broad strokes, energy status is reflected in fat stores and lean mass is indicative of protein stores. Body composition at the elemental or molecular level (see body composition models above) is affected by nutrient intake, absorption, utilization, storage and excretion. Essential nutrients are required for normal growth and cell functioning and normal body composition; when severe nutrient deficiencies exist, body composition is altered. For example, severe protein malnutrition leads to muscle wasting and altered fluid balance. Milder nutrient deficiencies may have direct or indirect effects. Inadequate calcium intake or absorption, or increased calcium excretion during growth results in suboptimal bone mineral accrual, thereby lowering peak bone mass and increasing the risk of fracture in childhood and later in life.[75] Depletion of total body iron stores from inadequate iron intake resulting in iron deficiency anemia in children is associated with lethargy and poor cognitive development, which in turn limits a child's engagement in usual childhood physical activities that would promote muscle and bone growth.[76]

The association between diet patterns (as opposed to individual nutrients) and body composition is less well defined. On average, vegetarians have less body fat then omnivores, and vegans, who exclude all animal products from their diet, are leaner still than both vegetarians and omnivores. Vegetarians and vegans are also known to have lower blood pressure and cholesterol. It is uncertain whether these health effects are directly related to diet or mediated by differences in body composition and lifestyle. Both lower body fat and improved bone mineral accrual are associated with diets rich in dark-green and deep-yellow vegetables and low in fried foods.[77] High energy intake, consumption of energy dense, highly processed foods, low fruit and vegetable intake, and consumption of sugared beverages have been associated with excess adiposity.[78] Interestingly, a composite measure of diet quality, the Healthy Eating Index, was not associated with BMI in the NHANES cohort.[79] However, a study of pregnant women in Singapore showed that adhering to a healthy diet quality was associated with lower adiposity and greater linear growth of offspring at birth.[80]

Energy undernutrition, body composition and health outcomes

Chronic undernutrition results in smaller body size and delayed maturation. Provided the undernutrition is chronic and not acute, weight-for-height relationships, such as BMI, are preserved in children. However, in the long run, chronic undernutrition can result in increased morbidity and mortality, especially among younger children, and reduced play, physical activity and work productivity at older ages.[81] For example, among school-aged

boys in Colombia, the group of poorly nourished boys had less spontaneous physical activity than adequately nourished boys.[82] Undernutrition also is associated with increased fat accumulation on the trunk and chronic cardiometabolic complications, such as insulin resistance, hypertension, and dyslipidemia later in adulthood.[83]

With more severe energy undernutrition, energy (fat mass) and protein (lean mass) reserves of the body become depleted. Among children being admitted to hospital, skeletal muscle depletion results in greater risk of morbidity and mortality.[84] Muscle mass deficits may also have a sustained negative effect on growth and quality of life.[85] Paradoxically, infants born to undernourished mothers are born small, have greater subcutaneous and intrabdominal body fat, and are prone to insulin resistance later in childhood.[86]

Reduced lean mass, or sarcopenia, can also occur in the context of disease. Cachexia, or muscle wasting with weight loss and poor appetite occurs in the context of chronic disease or cancer. Sarcopenia is loss of skeletal muscle mass and strength that occurs with aging or immobility. In children, muscle loss or deficits and reduced muscle strength occurs in inflammatory conditions, and neuromuscular, mitochondrial and metabolic disorders of childhood. In adults, the condition of *sarcopenic obesity* has been recognized as muscle deficits in the context of obesity, and it is predictive of poor physical functioning and disability.[87] More research is needed to understand the impact of skeletal muscle deficits in children.

The first 1000 days of life and the dual burden of malnutrition

The first 1000 days of life (conception to age two years) have been identified as a critical period for health outcomes later in life, including excess adiposity and related cardiometabolic complications. *In utero* exposures, such as maternal obesity and excess gestational weight gain, maternal diet, depression, exercise, smoking, and low vitamin D status have been linked to obesity risk of offspring. Early postnatal factors associated with excess adiposity later in childhood include duration of breastfeeding, antibiotic exposure, introduction to complementary foods prior to age 4 months, and rapid infant weight gain.

In resource poor areas with chronic undernutrition, the first 1000 days is important for promoting optimal birth outcomes, cognitive and motor development, lean mass accrual and work capacity. Nutritional restriction during pregnancy results in low birthweight, a risk factor for subsequent infant morbidity and mortality, and stunted linear growth. The importance of adequate nutrition during pregnancy was demonstrated by long term follow-up of a nutritional supplementation study that was done in Guatemala from 1969 to 1977. This study showed the greatest benefit to children whose mothers received a protein and energy supplement throughout pregnancy, as compared to the low energy/low protein supplement and those who received the supplement only as children.[88] The benefits were

multifaceted and included improved growth in early childhood, greater height and lean mass among adolescent girls, work capacity among males, and a variety of intellectual skills.

In resource poor areas, the manifestations of child stunting, wasting and micronutrient deficiencies coexist with increasing prevalence of overweight and obesity. The availability of energy dense, nutrient poor foods in combination with increasing sedentary lifestyles is now recognized as *the dual burden of malnutrition*. This dual burden can exist at the community level, with high rates of childhood stunting and obesity, at the household level, with stunting and obesity occurring in different generations, or at the individual level, when obesity co-occurs with stunting and/or micronutrient deficiencies such as iron deficiency anemia.[89]

Prevalence and health consequences of obesity and altered body composition

Among children, obesity is defined as having a BMI greater than the 95th percentile for age and sex, and overweight is defined as having a BMI between the 85th and 95th percentiles for age and sex.[10,90] Excess adiposity has reached epidemic proportions among children and adults in most high income countries and is increasing rapidly in many low and middle income countries. In the US, most recent data show that over the past 10 years (from 1999 through 2018) the prevalence of excess weight for length or obesity among children younger than 6 years has been stable, but still occurs at an alarming rate of 8.9−13.7%. For children 6−11 years of age, obesity has increased from 15.8% to 19.3%, but the prevalence of severe obesity (greater than or equal to 120% of the 95th percentile on the CDC 2000 BMI charts) was stable. However, among 12−19 year olds, the prevalence of both obesity (16.0%−20.9%) and severe obesity (5.3%−7.6%) increased in prevalence, particularly among Mexican American youth (22.3%−30.6% for obesity and 7.6%−12.9% for severe obesity).[91]

The prevalence of pediatric overweight and obesity is on an upward trajectory in many low and middle income countries, but is highly variable between and within countries. Appropriately collected data in many countries is lacking, and may be biased by sampling methods. One global study of children less than 5 years of age estimated that the average prevalence of overweight increased from 5.2% to 6% from 2000 to 2017.[92] A synthesis of 68 studies in Sub-Saharan Africa found that the proportion of school age boys who were overweight/obese was 7.6% and for girls, was 15.4%, while the proportion of those classified as obese was 2.0% and 3.9% in boys and girls, respectively. Analysis of time trends indicated a significant increase in the proportion of overweight/obesity over time.[93]

The health consequences of overweight and obesity in childhood and adolescence are also increasingly apparent. In children, the health risks associated with obesity include bone

and joint disease, emotional health, increased blood pressure, serum cholesterol, and insulin resistance, as well as increased risk of non-insulin dependent diabetes.[94] The greatest health risk of childhood overweight and obesity is the increased risk of morbidity and mortality later in life. Globally, the main causes of BMI-related years lived with disability were cardiometabolic (ischemic heart disease, stroke, diabetes mellitus, hypertensive heart disease), chronic kidney disease, and low back pain. Worldwide, deaths and years living with disability due to high BMI and its complications more than doubled from 1990 to 2017.[95]

Fat distribution as a correlate of diseases

The distribution of fat on the body represents a risk factor for certain diseases that is independent of total body fat. In particular, the tendency to accumulate fat on the upper trunk is associated with non-insulin dependent diabetes, hypertension and gall bladder disease. Both the total amount of fat and fat patterning were associated with cardiovascular risk factors (lipid profiles and blood pressure) in a large, multi-ethnic sample of boys and girls participating in the National Heart, Lung, and Blood Institute Growth and Health Study.[96,97] Some studies specifically address the impact of a centralized fat distribution. For example, waist circumference and waist-circumference-to-height ratio are simple anthropometric indicators of fat distribution associated with cardiometabolic risk in children.[98] Advanced imaging methods to measure intra-abdominal (visceral) adipose tissue in children and adolescents have shown that increased size of these fat depots is particularly harmful, being associated with insulin resistance, hepatic steatosis, elevated blood pressure, higher triglycerides and cholesterol levels, and metabolic syndrome.[99]

Physical activity and body composition

Physical activity and body composition have a synergistic relationship. Physical activity, especially weight-bearing activity, is important for growth and maintenance of muscle and for promoting the growth and strengthening of bone. The degree to which children meet recommended levels of physical activity is associated with BMI, subcutaneous and visceral adipose tissue levels and associated health outcomes.[100] Physical activity during growth has long-lasting beneficial effects into adulthood.[101] At the extremes of physical activity, with intensive training, subcutaneous fat stores may become depleted. Long distance running and ballet dancing, and other activities known for prolonged and intense training, are associated with significantly reduced fat mass. In females, these athletes often become amenorrheic and develop osteoporosis related to estrogen insufficiency. Sports that involve resistance training and high impact, weight bearing physical activity generally promote higher bone density.

Conversely, children with reduced physical activity who spend more time in sedentary activity have less lean mass, increased fat mass and a more centralized fat distribution.[102] Under extreme circumstances, as with children with severe quadreplic cerebral palsy who are unable to walk, lack of physical activity results in markedly reduced growth of lower limbs, reduced muscle and fat stores, and low bone mineral content and bone density. Children with diplegic or hemiplegic cerebral palsy have deficits in body composition commensurate with their ability to ambulate and bear weight. Even among previously healthy individuals with normal physical activity patterns, prolonged bed rest results in muscle and bone atrophy. Astronauts in space living in a weight-less environment experience similar problems.

Summary

The composition of the human body is regulated by genes, but is sensitive to environmental, behavioral, and nutritional factors. Developmental exposures and their timing are also important, as shown by the studies of *in utero* exposures and the long term effects of physical activity on body composition and health. Body composition is also an integral part of human growth, maturation and senescence, and has a wide range of health implications. Assessment of body composition throughout the lifecycle is highly feasible, and there is a broad array of techniques that can be used in clinical, research and field settings to further understand the life cycle changes in body composition and their role in health and disease.

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Additional reading

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Web resources

Excellent interactive sites describing body composition methods: http://www.bcm.edu/bodycomplab/mainbodycomp.htm.
For more about the elemental composition of the human body: https://sciencenotes.org/elements-in-the-human-body-and-what-they-do/.

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THIRD EDITION

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