Indicators of biological maturation and secular changes in biological maturation

Gaston P. Beunen, Alan D. Rogol, and Robert M. Malina

Abstract

Commonly used indicators of biological maturation are discussed, including sexual, skeletal, morphological, and dental maturity, and the hypothalamus–pituitary–end organ axes that regulate the growth and maturation processes. Interrelationships among indicators and the tempo, timing, and sequence of maturational events are also considered. Environmental factors that influence the level of maturity at a given point in time and the process of maturation are also discussed: undernutrition, obesity, ethnic/racial background, social class, familial characteristics, climate, and altitude. Recommendations for the design of studies of maturational events are made, and an overview of secular changes before and after 1970 is provided. The review concludes with specific recommendations for the inclusion of a maturity indicator or maturity indicators in the construction of an international growth standard for preadolescent and adolescent children

Key words: Growth reference, hormones, maturity, secular change

The concept of biological maturation

Maturation is a process that marks progress toward the adult (mature) state. Maturation is a process, whereas maturity is a state. All tissues, organs, and organ systems of the body mature, but they do so at different times and rates. As a result, assessment of biological maturity status varies with the bodily system considered. Of necessity, therefore, the concept of maturation is operational. The more commonly used systems for the assessment of maturation are the skeletal, reproductive (sexual), and somatic systems; hence, the terms skeletal, sexual, and somatic maturation are standard in the growth literature. Dental maturation (eruption and calcification) is occasionally used, but it tends to proceed independently of the other three systems. Biochemical and hormonal maturation, as steering mechanisms for the other systems, must also be considered.

Maturation of different systems tends to proceed independently of chronological (calendar) age, so that chronological age is not a good indicator of biological maturity. Nevertheless, the growth and maturity status of an individual or sample of individuals is routinely placed in the context of chronological age.

In constructing objective, reliable, and valid indicators of biological maturity status, it is of importance that the indicators reflect the maturation of a biological system, occur in all individuals as they progress toward the adult state, and reach the same endpoint, i.e., the mature or adult state. The indicators should also, to some extent, be independent of growth (size attained), i.e., they should not quantify the growth status of a tissue, an organ, or a biological system. Finally, a relevant indicator should be applicable throughout the entire maturation process, but the reality of variation among systems precludes this criterion [1–6].

Indicators of biological maturation

Skeletal maturity

The maturation of the skeleton is widely recognized as the best single indicator of maturity status [6]. All children start with a skeleton of cartilage and progress

Gaston P. Beunen is affiliated with the Department of Biomedical Kinesiology, Faculty of Kinesiology and Rehabilitation Sciences, Katholieke Universiteit Leuven, Leuven, Belgium; Alan D. Rogol is affiliated with the Department of Pediatrics, University of Virginia, Charlottesville, Virginia, USA; Robert M. Malina is affiliated with Tarleton State University, Stephenville, Texas, USA.

Please direct queries to the corresponding author: Gaston P. Beunen, Department of Biomedical Kinesiology, Faculty of Kinesiology and Rehabilitation Sciences, K.U. Leuven, Tervuurse vest 101, B3001, Leruven, Belgium; e-mail: gaston.beunen@faber.kuleuven.be.

toward the fully ossified, adult axial skeleton. In the case of the tubular bones (long and short bones), maturity is attained when the epiphyses are fused with their corresponding diaphyses; in the case of round or irregularly shaped bones, maturity is defined by adult morphology (shape). The bones comprising the craniofacial skeleton differ in embryonic origin, and their growth and maturation are approached differently. They are not considered in this discussion of skeletal maturation.

The bones of the hand and wrist provide the primary basis for assessing the maturity status of the child, although the knee, hip, and foot have also been used. The progress of maturation of the skeleton is ordinarily monitored with standardized radiographs, and assessment of maturity is based on changes occurring from initial ossification to adult morphology of individual bones. Criteria for individual bones are characterized as maturity indicators—specific features of individual bones that are universal and occur regularly in a definite, irreversible order. Three methods for the assessment of skeletal maturity—the Greulich-Pyle, Tanner-Whitehouse, and Fels methods—are commonly used at present.

The *Greulich–Pyle method* [7] is based on the original work of Todd [8], and it is sometimes called the atlas or the inspectional technique. The atlas consists of sex-specific radiographs representative of the maturity status at a given chronological age from birth to 19 years. The radiograph that was most typical of about 100 radiographs of each sex at each age level was selected as the reference plate. Each bone on the standard plates represents its median appearance at a given chronological age (however, in some plates of the atlas, there is considerably variation for a given chronological age). The method is based on the radiographs of a large sample of children from the Brush Foundation Study. The children were from families of high socioeconomic status in Cleveland, Ohio, USA.

The skeletal maturity of a child is determined by comparing his or her hand-wrist skeleton to the standard plates of the atlas. Skeletal maturity is expressed as a skeletal age. There is, however, variation in how the method is applied. Quite often, the assigned skeletal age is that of the plate which most closely matches that of the child. This overlooks variation among bones in the hand-wrist and also variation among standard plates. More appropriately, the method should be applied by matching each individual bone to the atlas plates. Accordingly, the skeletal age of the plate with which the individual bone most closely coincides is noted, and the skeletal age assigned to the child is the median value of the skeletal ages of all bones [9].

The *Tanner–Whitehouse method* is sometimes called the bone-specific approach [10, 11]. Maturity indicators were defined and described for each bone. Each indicator is expressed as a stage from initial ossification to union (radius, ulna, metacarpals, phalanges) or adult morphology (carpals), and a point score is assigned to each stage. Twenty bones are used: the radius, ulna, seven carpals (excluding the pisiform), and the metacarpals and phalanges of the first, third, and fifth digits (rays). The scores are summed and can be expressed either as a maturity score or as a skeletal age. The maturity scale (0 to 1,000) was constructed to minimize the overall disagreement between the results from the long and the round bones.

The first version of the method (Tanner–Whitehouse I) [10, 11] provided a skeletal age based on the sum of maturity scores for 20 bones. The second version (Tanner–Whitehouse II) [12] provided three different scales and skeletal ages: a 20-bone scale, an RUS (radius, ulna, short bones) score (13 bones), and a CARP scale for the seven carpal or round bones. Both the Tanner–Whitehouse I and the Tanner–Whitehouse II skeletal maturity references are based on a sample of about 3,000 healthy British children. In the second version, the final stage of a number of bones was no longer assessed, and the scoring system was modified, but the maturity indicators were not changed. The third version of the method (Tanner–Whitehouse III) [13] considers only the RUS and carpal bones and no longer includes a 20-bone skeletal age, and the reference values are now based on samples of British, Belgian, Italian, Spanish, Argentinean, US (a well-off sample from the suburbs of Houston, Texas), and Japanese children.

The *Fels method* is bone-specific and is based on a sample of middle-class children from south-central Ohio, USA, enrolled in the Fels Longitudinal Study [14]. The authors defined an extensive series of maturity indicators for all bones of the hand-wrist skeleton [14]; ratios between linear measurements of epiphyseal and diaphyseal widths for individual long bones were included among the indicators. The potential of each indicator was tested on its ability to differentiate between individual children of the same chronological age and on its universal appearance, reliability, validity, and completeness. The resulting Fels method is based upon the final grading of 85 grade maturity indicators for the radius, ulna, carpals, metacarpals, and phalanges, and 13 measured ratios of epiphyseal and diaphyseal diameters of the radius, ulna, metacarpals, and phalanges. The number of indicators to be assessed at a given chronological age varies with chronological age and sex and is relatively large at some ages; however, most indicators are assessed simply as present–absent or maximally on a five-grade scale. The chronological age and sex of the child and the ratings and ratios are entered into a microcomputer, which calculates a skeletal age and associated standard error of estimate.

Other methods for the assessment of skeletal maturity have been proposed. Some are of historical interest, and others are less commonly used [3, 6]. At present, several computer-based protocols have been applied to

the Tanner–Whitehouse II method, and the experimental results are reasonably consistent with the ratings of expert assessors [15, 16].

The three currently used methods for the assessment of skeletal maturity are similar in principle but differ in maturity indicators, scales of maturity (scores, skeletal age), and reference samples. The Greulich–Pyle and Fels methods provide a single skeletal age, whereas the Tanner-Whitehouse method provides several skeletal ages. A skeletal age corresponds to the level of skeletal maturity attained by a child relative to the reference sample for each method. Given differences in the methods and in the reference samples for each, skeletal ages derived from each are not equivalent. In fact, the skeletal maturity status of a child rated by all three methods may be quite different [1, 3–5, 17]. Regardless of the method used, quality control in assessment is essential. Variation within and between assessors can be considerable and should be reported.

Skeletal age has limited utility by itself. The utility of skeletal age as a maturity indicator is based on its relationship to a child's chronological age. Skeletal age may simply be compared with chronological age, may be expressed as the difference between skeletal age and chronological age (i.e., skeletal age minus chronological age), or may be expressed as a ratio of skeletal age to chronological age. There is considerable variation in skeletal age at each chronological age level. The standard deviations of the RUS bone age (Tanner–Whitehouse III) is approximately 1 year from the age of 5 years in both sexes to 14 years in girls and to 16 years in boys (Tanner et al. [13], p. 10).

The advantages of skeletal maturity as an indicator of biological maturity are several: it gives reasonably precise and reliable estimates, is applicable throughout the postnatal maturation period, and reflects maturation of an important biological system. Its disadvantages are that it involves exposure to low-level radiation, it requires training and quality control, and the stages (maturity indicators) are somewhat arbitrary and suggest discrete steps in a continuous process [1, 3–5].

Sexual maturity

Sexual maturation is a process that extends from the early embryonic differentiation of the sexual organs to full maturity of these organs and fertility. Puberty is a transitional period between childhood and adulthood during which the sex organs and the reproductive system mature and the growth spurt takes place. Major psychological, behavioral, cognitive, and emotional changes also occur during puberty. Individual differences in timing and tempo are considerable at this time.

The assessment of sexual maturation is based on secondary sex characteristics: breast development and age at menarche in girls, genital (penis and testes) development in boys, and pubic hair in both sexes. Development of the breasts, genitals, and pubic hair is most often rated on five-point scales described by Tanner [5]. The stages should not be identified as "Tanner stages" but as stages of sexual maturation with identification of the specific characteristic(s) (breast, pubic hair, or genitals) assessed. The stages of each characteristic are neither equivalent nor interchangeable. Stage 1 of each characteristic indicates the prepubertal state (absence of development) and stage 2 the initial, overt development of each characteristic that marks the transition into puberty. Stages 3 and 4 mark progress in maturation, and stage five 5 indicates the adult (mature) state.

Ratings of stages of secondary sex characteristics are ordinarily made by individual observation at clinical examination. Sometimes, as in the Harpenden Growth Study [18, 19], the examination was made from standardized, nude photographs. In nonmedical settings, self-assessments by youths are increasingly used. Self-assessments should be done privately in a quiet room using good-quality photographs of the stages and simplified descriptions. There is obviously a need for quality control (intra- and interobserver reliability), and in the case of self-assessment concordance with experienced assessors should be verified. Overall reproducibility by experienced assessors is generally good, with about 80% of agreement in assigning the stages, although some studies report a percentage of agreement as low as 40% [3].

Age at menarche, the first menstruation, is perhaps the most widely monitored secondary sex characteristic in females. It can be obtained in three different ways: prospectively (longitudinal design), by interrogating the same girls at regular intervals of 3 to 6 months; retrospectively, by interrogating postmenarcheal girls or women and asking them to recall when they experienced their first menstruation; and status quo, by interrogating large samples of girls approximately 9 to 16 years of age about their menarcheal status (i.e., pre- or postmenarcheal, see below). The first two methods provide ages at menarche for individuals, whereas the status quo method provides an estimated age at menarche for a sample and does not apply to individuals.

Other secondary sex characteristics include axillary hair in both sexes and facial hair and voice change in boys. As a rule, these are late-developing indicators during puberty and are not widely used in studies of biological maturation. A more direct estimate of genital maturity in boys is provided by testicular volume. The method is used primarily in the clinical setting and requires a series of ellipsoid models of known volume, which have the shape of the testes (Prader orchidometer) [20, 21]. The models range in volume from 1 to 25 ml; a volume above 4 ml marks the beginning of puberty.

The ages at which specific stages of sexual maturity are reached are ordinarily derived from longitudinal studies in which children are examined at regular intervals, preferably every 3 months, starting in late childhood (prepuberty) and continuing through puberty into early adulthood. Data obtained from prospective studies provide estimates of the age at initiation of a stage and duration of a stage. Mean ages and associated standard deviations can be calculated. Such longitudinal studies require, of course, long examination periods and are most often restricted in sample size and representativeness of the sample. Cross-sectional designs (status quo) provide ages of "being in a particular stage." Two pieces of information are needed: the exact chronological age of the child and whether or not the child is in a particular stage of sexual maturation or, in the case of girls, pre- or postmenarcheal. The percentages of children in a particular stage at each age are used with probits or logits to obtain sample statistics (median, means, and standard deviations) for each stage of a characteristic or for age at menarche. The percentages of individuals in each stage of a secondary sex characteristic increase with chronological age, and the maturity curves have a sigmoid shape.

Secondary sex characteristics are reasonably easy to determine, reflect an important biological system, and are closely related to underlying hormonal axes. On the other hand, secondary sex characteristics have limitations, in that the stages are somewhat arbitrary and discrete, they are limited to puberty, and the method of assessment is invasive in nonclinical settings (not necessarily true for self-assessment). Moreover, the use of secondary sex characteristics may have associated sanctions among some cultural groups.

Biochemical and hormonal maturity

Growth and adolescent maturation surely depend on specific hypothalamic–pituitary–end organ axes. The process of fetal growth does not depend very importantly on the fetal hypothalamic–pituitary function; however, the process of fetal differentiation does.

Hypothalamic–pituitary–thyroid axis

The physiological maturation of the thyroid is apparent as early as the 8th week of gestation [22]. By the 10th to the 11th week, iodine trapping and synthesis of thyroid hormones occur. Until birth the metabolically inactive reverse triiodothyronine (rT_3) predominates, only to be followed by a large burst of thyrotropin (TSH) secretion just after birth and a switch to the more metabolically active T_3 by a specific deiodinase enzyme. There are only slight differences in the normal thyroid axis hormone levels in the first year or two of life compared with levels in the adult. The hormone levels then remain virtually the same until puberty, when estrogen raises thyroxin-binding globulin (TBG) levels. Although thyroid hormones are not responsible for the pubertal growth spurt or sexual maturation, they are thought to be permissive for these processes. Adequate thyroxin is necessary for normal growth in infancy and childhood and also for growth hormone (GH) gene expression, and thyroxin may also act directly on cartilage [23].

Hypothalamic–pituitary–adrenal axis

The hypothalamic–pituitary–adrenal axis shows hormonal activity beginning between the 8th and 12th weeks of gestation. Corticotropin-releasing hormone (CRH) from the hypothalamus regulates the growth of pituitary corticotrophs, adrenocortical differentiation, and steroidogenic maturation of the fetal hypothalamic–pituitary–adrenal axis. The adrenal gland at birth is composed mainly of the definitive (mineralocorticoid) and the very much larger fetal dehydroepiandrosterone (DHEA) zones. As the child matures, the adrenal gland forms a focal reticular and then a continuous reticular zone. It is this zone that makes adrenal androgens under the stimulus of corticotropin and perhaps other adrenal androgen-stimulating hormones. The process of *adrenarche* marks the transition of this zone as it releases greater and greater quantities of the adrenal androgens, DHEA and its sulfate (DHEA-S), and androstenedione, precursors of both more potent androgens (testosterone) and estradiol. There is a steep rise, perhaps 4- to 50-fold, in DHEA-S and androstenedione secretion. Adrenarche usually occurs at the same time as the mid-childhood growth spurt and together with the preadolescent fat spurt. This process is independent of gonadotropin-induced "true" puberty. However the mid-childhood growth spurt is of much less magnitude than the pubertal growth spurt (see below) and is quite variable in its timing, tempo, and magnitude, depending on the state of pubertal gonadal development. It is not a useful parameter for linking linear growth to the "biochemical" (e.g., hormonal) measurements.

Hypothalamic–pituitary–gonadal axis

Sexual determination (testicular development) occurs at conception. Sexual differentiation (genital development) is the process by which the manifestations of that determination become overt. Male sexual differentiation requires the expression of the product of the sex-determining region on the Y chromosome (SRY) to select the pathway that the bipotential gonad containing the Wolffian and Mullerian ducts and the external genitalia will take. The embryonic gonad differentiates along one or the other pathway beginning at approximately the sixth week of gestation under the influence of gene products of the sex chromosome and autosomes. Mutations in a number of transcription factors, for example, SRY, SOX9, and SF-1, may affect testicular determination [24]. Sexual differentiation

continues with stimulation of the Wolffian ducts and regression of the Mullerian structures in boys. The former are stimulated directly by testosterone to form the vas deferens, epididymis, and seminal vesicles. Testosterone also potentiates the effects of anti-Mullerian hormone (AMH), also known as Mullerian inhibiting substance (MIS), to permit complete regression of these structures.

The male external genitalia require dihydrotestosterone (DHT) for full development. If this does not occur, the labial scrotal folds do not fuse completely and there is not an intact penile urethra.

Defects in testosterone production cause undervirilization of 46, XY infants. Before 10 weeks of gestational age, very little androgen production occurs. The critical period for androgen production (and action) occurs between the 10th and 20th fetal weeks, when the Leydig cell is dependent upon stimulation by luteinizing hormone (LH) and human chorionic gonadotropin (hCG). In the male fetus, the lack of full production of testosterone may lead to a genital phenotype ranging anywhere from that of a normal female to that of an incompletely developed male, with microphallus, scrotal hypoplasia, and undescended testes

In the first few days following delivery, the initially "high" levels of testosterone decline, only to rise again to approximately 8 nmol/L (230 ng/dL) sometime between weeks 3 and 12 [25]. These levels may be important for further alteration in genital development (for example, the priming of androgen target tissues for subsequent androgen-mediated growth and maturation) and/or brain development (for example, permanent virilization of the hypothalamus so that it secretes LH tonically, rather than cyclically as in the female [26]).

During the quiescent period between the neonatal–early infancy surge and pubertal development (the so-called *prepubertal hiatus* or *juvenile pause*), the full complement of structures and pathways for androgen synthesis, secretion, and action are present but are active at a very low level. Disorders of advanced puberty, e.g., central precocious puberty or peripheral "pseudo" puberty, may occur during this phase.

At puberty the levels of testosterone rise exponentially as the hypothalamic–pituitary–gonadal axis regains the active state. At first there are only small LH pulses, which cause the testis to produce small, but measurable, levels of testosterone. Since the negative feedback control system is operative at the (nearly) prepubertal, very sensitive range, these low levels of testosterone are capable of reducing gonadotropin-releasing hormone (GnRH) secretion and thus reducing LH release. As the boy matures, the GnRH pulse generator operates more like the adult generator, and the low, but rising, levels of testosterone are no longer able to have such exquisite negative feedback control. The sum of these two processes is increasing testosterone production, at first only at night (with the first pulse early in the first episode of deep sleep), and then into the day, but with a very distinct variation between day (early morning) and night, which may be as high as 10-fold. With "complete" maturation, there are fluctuations in testosterone concentration (perhaps 40%) during the 24 hours and a small diurnal variation, with the highest levels in the early morning.

Hypothalamic–pituitary–GH–IGF-I axis

GH is synthesized and secreted by 8 to 10 weeks of gestation, peaks at mid-trimester, and then decreases until delivery. The growth of the fetus is not particularly sensitive to the GH–insulin-like growth factor I (IGF-I) axis, since congenitally hypopituitary children have only a minor decrease in birth length. At birth the axis is quite active, with pulsatile GH release at relatively high amplitude. Throughout infancy and childhood, GH and its stimulation of IGF-I production are responsible (with adequate thyroid hormone levels) for the relatively constant growth rate. At puberty there is a marked increase (approximately 2.5- to 3.5-fold) in GH and IGF-I production, secondary to the estrogen-induced increase in pulsatile GH release. The levels of IGF-I may be 5- to 10-fold those of younger children and adults, especially during the period around PHV. The levels of GH (mean 24-hour production) and IGF-I peak coincidentally with peak height velocity (PHV) [27]. The variability in the release of these hormones precludes a simple relationship of their individual levels with height velocity; however, the mean levels over 24 hours correlate reasonably well, but not so tightly as to predict the attainment, timing, or tempo of PHV or of adult height.

Changing hormonal levels provide direct evidence of the maturation of specific structures and tissues that underlie the overt manifestations of biological maturation that are commonly assessed in growth studies, i.e., skeletal age, secondary sex characteristics, and adolescent growth spurt (see below). However, most of the hormones directly related to maturation are produced in a pulsatile manner, so that serial blood samples taken over relatively long periods (e.g., 8 or 24 hours) are required to adequately evaluate the hypothalamic-pituitary-end organ axes. For example, it is the increase in the pulse amplitude of GnRH that permits the increase in LH that drives the increase in testosterone and estradiol at puberty. Moreover, the collection of blood samples and associated assays require specialized equipment that precludes their use in large-scale surveys. Static levels of the steroid hormones may be measured in saliva or blood samples and may serve as "anchors" for several of the stages of adolescent development. The more recent third- and fourth-generation gonadotropin assays may permit the distinction of hypogonadotropic individuals from those who are normal, but prepubertal.

Somatic or morphological maturity

Body size by itself is not a valid indicator of biological maturity, since the adult state is not the same for all individuals. As such, it is not appropriate for use as an indicator of biological maturation. Concepts such as height age, i.e., the corresponding chronological age at which, in a population, a specific stature is on average attained, are not useful maturity estimates.

If longitudinal height data that span late childhood through adolescence are available, the characteristics of the adolescent growth spurt can provide two indicators of somatic maturity: age at the onset of the growth spurt in height (first inflection point of the adolescent growth curve, takeoff) and age at maximum velocity (second inflection point of the adolescent growth curve, PHV). Corresponding parameters of the growth spurt can also be derived for other linear measurements, e.g., sitting height and leg length.

If adult height is available (as in longitudinal studies), the percentage of adult height attained at a given age or the age at which a certain percentage of adult height is attained can be used as a maturity indicator. To accurately estimate the parameters of the growth curve, careful measurements that span adolescence and that are taken at regular intervals, at least two times per year (preferably three or four times a year), are needed. Curve-fitting techniques based on structural and nonstructural models have facilitated estimation of the parameters [28–30].

Structural models have a preselected form of the growth curve, and the mathematical parameters of the model have a predetermined biological meaning. Nonstructural models do not have a predetermined form, and the parameters may not be easy to interpret biologically.

The assessment of somatic maturity based on the parameters of the growth curve (age at onset and age at maximum velocity) is limited to the adolescent period, and only one or two biological events are considered. As noted, their derivation requires longitudinal measurements of individual children over a relatively large age span, but they do provide an accurate estimate for a major event in the pubertal period.

Percentage of adult height is calculated from present height and adult height. Adult height is measured if children are followed until adult stature is attained or can be estimated. Prediction formulas are available for European and American samples but have not been validated on other populations [9, 11–13, 31–33]. Attempts have also been made to predict adult stature without skeletal age [34, 35].

Use of the percentage of adult height as an indicator of somatic maturity is an indirect technique that requires the estimation of skeletal maturation, at least for the most accurate systems. It can, however, be applied throughout most of the maturation period, beginning in childhood, and reflects the progress toward maturity of an important biological characteristic.

Dental maturity

Dental maturity has been traditionally estimated from the ages of eruption of the deciduous and/or permanent teeth, the number of teeth present at a certain chronological age, or the age at which a specific number of teeth has erupted [36]. Eruption is only one event in the calcification process of teeth and has limited biological meaning. Moreover, the criteria for eruption (e.g., initial piercing of the gum line to complete eruption) vary.

Dental calcification, as evaluated on radiographs, also provides an indication of maturity status. Demirjian et al. [37] developed a scale of dental maturity based on the principles of the Tanner-Whitehouse [10] method for the assessment of skeletal age. The procedure requires panoramic radiographs of the seven teeth in one quadrant of the mouth (two incisors, the cuspid, two premolars, and the first and second molars). As in the Tanner–Whitehouse system, specific maturity indicators are identified for each tooth, the stages are scored on a maturity scale for each tooth, and the scores are subsequently summed to provide an overall dental maturity score.

Eruption and calcification of the teeth reflect the maturation of the dentition. Deciduous teeth erupt between about 6 and 30 months, and permanent teeth (excluding the third molars) erupt between about 6 and 13 years. Calcification of the permanent dentition begins in late gestation and continues to about 16 years, on average. Similar to the criteria for skeletal and sexual maturity, the stages of calcification are discrete and the criteria are somewhat arbitrary. The sex difference in dental maturation is less pronounced than for other maturity systems [38].

Correlations between dental (based on calcification, Demirjian method) and Tanner–Whitehouse I skeletal ages are generally low in children 7 to 13 years of age [36]. Dental maturity (the ages at which individuals attain 14, 20, and 26 permanent teeth) is generally independent of sexual, skeletal, and somatic maturity during male adolescence [39].

Interrelationships among maturity indicators

The issue of interrelationships among the various indicators of biological maturation is complex, because only skeletal maturity and percentage of adult stature span the entire maturation period from birth to adulthood. Indicators such as age at PHV, stages of sexual maturation, and age at menarche in girls are limited

to puberty. A cluster analysis of 21 maturity indicators (skeletal, sexual, somatic, and dental) assessed in a sample of 111 Polish boys followed longitudinally from 8 to 18 years identified a general maturity factor during adolescence. This general factor included ages at peak velocity for several linear dimensions, attainment of stages of sexual maturity, skeletal ages of 14 and 15 years, ages at attaining 90%, 95%, and 99% of adult stature, and age at onset of the growth spurt in height. Correlations among these indicators were high; none was below 0.70 and many were above 0.80. This suggests central regulation of the timing of the growth spurt and sexual maturation by the nervous system and corresponding hormonal correlates.

The second and third factors were related to indicators associated with prepubertal maturity (skeletal age of 11 and 12 years, 80% of adult height) and the ages by which 14, 20, and 26 teeth had erupted [39]. Similar results were obtained in Polish girls [40] and in American boys and girls [41], although indicators of dental maturity were not included in these analyses. The clustering of prepubertal maturational events that are somewhat independent of the clustering of pubertal events suggests that different hormonal and related growth factors are the driving forces that underlie these events. In general, it is the hypothalamic–pituitary–GH/IGF-I and the hypothalamic-pituitary-gonadal axes, but especially their interactions, that drive adolescent growth and maturation, given adequate thyroid status.

Indicators of skeletal, somatic, and sexual maturity are thus related during adolescence. When children are grouped according to an event of sexual maturation, the mean chronological age and the skeletal age at reaching that event are generally quite similar, but the standard deviation in skeletal age at reaching the event is markedly reduced. There is more variation in chronological age than in skeletal age at the time of menarche and at the time of PHV [3].

Timing, sequence, and tempo of maturational events

Overview

The mean and median ages at reaching various stages of somatic and sexual maturation are summarized in **tables 1** and **2**, respectively. The age at takeoff of the adolescent growth spurt averages

TABLE 1. Mean age (years) at takeoff and at peak height velocity (PHV) in samples of European and North American adolescents[a]

	Girls		Boys	
Population	Takeoff	PHV	Takeoff	PHV
Europe	8.2–10.3	11.4–12.2	10.3–12.1	13.8–14.4
North America				
Caucasian	8.7–9.6	11.3–12.0	10.5–11.4	13.3–14.1
African-American	8.9	10.8	10.3	14.3

a. Adapted from Malina et al. [3, 42] and Beunen and Malina [43].

TABLE 2. Median/mean ages at the onset of stages of sexual maturation in samples of European and North American adolescents[a]

	Girls' breast stage		Girls' pubic hair stage	
Population	B2	B5	PH2	PH5
Europe	10.0–11.6	14.0–15.7	10.4–12.1	13.6–15.4
North America				
Caucasian	10.0–11.2	13.7–15.5	10.5–11.6	13.1–16.3
African-American	8.9–9.5	13.9	8.8–9.5	14.7
Mexican-American	9.8–10.9	14.7	10.4–10.5	15.5–16.3
	Boys' genital stage		Boys' pubic hair stage	
Population	G2	G5	PH2	PH5
Europe	10.8–11.4	14.9–16.1	11.5–13.4	14.9–16.0
North America				
Caucasian	10.0–11.8	14.3–17.3	11.2–12.2	14.3–16.1
African-American	9.2	15.0	11.2	15.3
Mexican-American	10.3–12.4	15.8–16.3	12.3–16.3	15.7–16.1

a. Adapted from [3].

between 8.0 and 10.3 years in samples of European and North American girls, and the age at PHV is about 2 years later (10.8 to 12.2 years). Corresponding maturational events occur about 2 years later in boys. The standard deviations of the somatic maturity characteristics vary between 0.7 and 1.2 years, indicating a high degree of interindividual variation in the timing of the growth spurt. The mean age ranges of boys and girls from Europe and North America (Caucasian, African-American) overlap.

The mean or median ages at reaching breast stage 2 (B2) vary between 8.9 and 11.6 years and are earlier in African-Americans. Similar ethnic differences are apparent for breast stage B5 and pubic hair stages PH2 and PH5. B2 is, on average, the first overt sign of puberty in girls, and genital stage 2 (G2) is the first overt sign in boys. G2 occurs between the ages of 9.2 and 12.4 years and is also somewhat earlier in African-Americans. Note, however, that the appearance of pubic hair (PH2) may precede breast or genital development. The standard deviations of age at reaching stages of sexual maturation are generally larger than those for age at PHV and are larger for the more advanced stages. The latter may reflect difficulties in assessing stages 3 through 5 of breast, genital, and pubic hair development. The average age at menarche is between 12.1 and 13.5 years in European and North American girls. African-American girls attain menarche earlier than Caucasian girls, and within Europe there is a north–south gradient, with the mean age at menarche declining from north to south. Variation within and between countries is relatively large, with standard deviations of about 1 year. It should be noted that interindividual variation within populations is considerable.

The transition from one stage to the next is an indicator of the *tempo* of maturation. However, longitudinal data documenting the duration of stages are very limited. The duration of the pubertal transition from G2 to G5, B2 to B5, and PH2 to PH5 is quite variable. The average duration was about 2.2 years for breast development and 2.7 years for pubic hair development in Swiss girls from the Zurich Longitudinal Study. The corresponding estimates for Swiss boys are, on average, 3.5 years for genital development and 2.7 years for pubic hair development. The standard deviation is about 1.0 year [44, 45]. Data from the Harpenden Growth Study indicate longer durations, 4.0 years for breast and 2.5 years for pubic hair development. Note, however, that the 95th percentile for breast development from B2 to B5 is almost 9.0 years, whereas the 5th percentile is 11.5 years [18]. Some of the extreme variation in the Harpenden Growth Study may be due to methodological limitations of assessing the development of secondary sex characteristics from photographs. The setting of the Harpenden Growth Study was a children's home. Although the children were well cared for at the home, most of them had probably lived under socially disadvantageous conditions early in life. It is, however, difficult to assess the impact of these disadvantageous conditions early in life on the timing and sequence of adolescent events, especially at the individual level. Nevertheless, the broad range of variation in timing and tempo implies major limitations on the use of the average sequence of development of biological maturity indicators.

Factors that affect the timing, sequence, and tempo of maturational events

Although the processes of biological maturation and corresponding indicators are under strong genetic control (see related chapter by Thomis and Towne [46] in this issue), a number of environmental factors are also associated with variation in maturation. Chronic undernutrition is perhaps the most significant. It is often associated with impoverished social and economic conditions. Other factors include social class variation in some developed countries, familial characteristics, climate, altitude, and disease.

Undernutrition is associated with later ages at PHV and menarche in rural areas of developing countries [3]. Skeletal age is more delayed relative to chronological age in undernourished than in well-nourished children [12]. There is, however, variation among studies in the extent of delay in skeletal age, depending on the method of assessment. For example, Fels skeletal ages are significantly delayed relative to Tanner–Whitehouse II skeletal ages and relative to chronological age in school-aged Mexican children living under impoverished health and nutritional circumstances [47]. The results suggest that some of the variation in skeletal maturity status among chronically undernourished children may reflect variation in methods of assessment.

Variation in maturity status between ethnic or racial groups is less pronounced than that within populations, especially variation between the undernourished and well-nourished or between economic extremes. The mean age at menarche of well-nourished girls from Africa and Asia varies between 12.4 and 13.6 years, values similar to those observed in European and North American girls. However, the mean age at menarche of undernourished girls or girls living in rural areas in some developing countries varies between 13.9 and 14.6 years [48, 49]. In reports published after 1980, differences in the mean age at menarche between African girls living in rural areas or under poor nutritional conditions and those from urban or better-off areas vary between 0.6 and 1.1 years. These differences are still larger than the differences in age at menarche between most African countries [50]. Similar but less pronounced differences have been reported for ethnic variation in skeletal age and age at PHV, but the data are limited to North America, Europe, and Japan [3, 51,

52]. Given ethnic or racial variation in maturity status, it is essential that samples from diverse populations be included in the development of an international growth reference. Presumably, the use of samples from North America or Europe, South America, Africa, and Asia (Near, Middle, and Far East) would result in a good representation for an international reference. The Tanner–Whitehouse III method [13] appears to be a reasonable international reference for skeletal maturity; it is based on samples from Europe (Belgium, Italy, Spain, and the United Kingdom), Asia (Japan), Latin America (Argentina), and North America (well-off children from the northern suburbs of Houston, Texas, USA).

Overweight and obesity result from an imbalance between energy intake and energy expenditure. Regardless of etiology, obesity is, on average, associated with advanced maturation among children and adolescents. Some evidence suggests that maturational timing apparently has a greater long-term effect on the level of fatness than the level of fatness has on maturational timing [53].

Although it is well documented that elite female athletes in several sports are characterized by late biological maturation, there is no convincing evidence that systematic physical activity or regular training for sports has a causal influence on the timing of maturation [1–3]. Chronically low energy availability, which is sometimes observed in elite athletes, may contribute to later maturation, but this has not been established [54]. Nevertheless, chronically low energy availability is probably a causal factor in the regulation of reproductive function in mature adolescents and adult women [54].

In contrast to measures of body size, variation in the ages at PHV and menarche associated with socioeconomic status is generally smaller. Among Polish and British youths, those from better-off socioeconomic circumstances attain PHV and menarche somewhat earlier than those from poorer conditions. However, the ages at PHV and menarche do not consistently differ among Swedish adolescents grouped according to socioeconomic status [3]. Urban–rural contrasts in indicators of maturity status are apparent in several European countries (e.g., Poland and Greece); they are negligible in others [3]. Urban–rural differences in less-developed countries are larger and probably reflect socioeconomic status and nutritional factors [55]. The age at menarche is also related to family size, increasing by 0.1 to 0.2 years for each additional sibling in the family among both nonathletic and athletic European and North American girls [56].

The mean age at menarche has a moderate negative correlation (–0.5 to –0.6) with the mean annual temperature of the habitat [57]. On the other hand, the association between altitude of residence and maturation varies among racial or ethnic groups. Children living at high altitudes in the Andes mature later than those living in the lowlands, but the opposite is observed in Ethiopia [3]. These observations may be explained, in part, by variation in living conditions (e.g., nutritional conditions, infectious disease load, and poor public health) associated with lower socioeconomic status in the ethnic groups residing at high altitude.

Since many of the factors that can influence biological maturation process are interrelated, it is difficult to partition independent effects. Nevertheless, factors that potentially have an adverse effect on maturity status should be considered in the inclusion or exclusion criteria in the development of an International Growth Standard for Preadolescent and Adolescent Children. This can be perhaps be achieved by selection of adequate subsamples.

Seasonal variation in maturity

Since information on the topic of seasonal variation in maturity is very limited [58, 59], it will not be covered in this review. Among Canadian boys and girls 8.5 to 18.0 years of age, about 67% and 60% of the yearly growth in height, respectively, was accounted for by summer velocities [60].

Design of studies of maturational events

On the basis of experience in planning studies of growth and maturation, present knowledge about variation in the timing and sequence of maturational events, and methodological considerations in constructing reference data [61], the following recommendations are offered:

» Cross-sectional designs can be used to construct reference data for maturational events using the status quo method [5];
» Longitudinal data are required to obtain precise information about growth and maturation patterns [5];
» Longitudinal observations made every 3 months are optimal for describing maturation during adolescence. It can be verified whether observations made every 6 months provide accurate data on maturation. This may be done by using already available longitudinal data from observations made every 3 or 4 months;
» Longitudinal observations should be made from preadolescence onwards. Given interindividual variation, the observations should start at a fairly early age, most likely from 8 years onwards in girls and starting a year later in boys. Some data indicate that a significant percentage of US girls may begin puberty at even earlier ages [62], which suggests that it may be advisable to start even at 6 years in girls and a year or so later in boys. If it is feasible, ultrasensitive estrogen assays based on molecular biological techniques can be used to accurately predict the onset of

pubertal development before the external signs (e.g., breast development) appear. This could considerably reduce the length of the follow-up needed to cover the adolescent maturation period;

» A pure longitudinal study over a relatively long period with four measurement periods per year may not be feasible; a multiple (mixed) longitudinal design may provide accurate results. Such a design could consist of a follow-up of birth cohorts 1 year apart that are followed over 1 year (with two or four measurements per year) or, more likely, several cohorts followed over 3 to 4 years with overlapping age levels (at least one age level). Again, the efficiency of such a mixed longitudinal design should be verified by data from pure longitudinal studies. The results of the simulated mixed longitudinal design should then be validated against the pure longitudinal data;

» The sample size depends on the variable, age, and percentiles required and whether the distribution is normal or can be normalized. For body-mass index (BMI), Guo* demonstrated that the confidence limits of 95th percentiles markedly decrease until the sample size reaches 200 subjects; see also the article by Cole [63] in this volume.

» A combination of cross-sectional and longitudinal designs should be considered.

Secular change in maturational events

Summary of secular changes until 1970

Most of the available evidence for secular changes in biological maturation is derived from records of the age at menarche. Data from retrospective and status quo techniques do not necessarily correspond closely [49]. Although most of the more recent publications are based on the status quo method, older data are partly or entirely based on retrospective data (for a more detailed discussion see Danker-Hopfe [64]).

The mean age at menarche in Norwegian girls was rather stable at 16 years in lower social strata and 14 years in higher social strata from 1820 to 1910–20 and declined subsequently to 13.3 years in the early 1950s [65, 66]. In the United States, the mean age at menarche declined from about 14.7 years in the 1870s to 12.8 in the 1950s [67]. Corresponding data for Japan indicate a decline from a bit over 16.0 years at the end of the nineteenth century to about 15.0 years in girls born around 1930 and subsequently to 13.0 years for girls born after World War II [3].

Recent secular trends in age at menarche

The trend toward earlier menarche has slowed or stopped in several countries. Since the 1960s, changes have been small in US girls, about 0.2 years in European Americans and about 0.4 years in African-Americans. The trend has also stopped or slowed in several European countries, such as the United Kingdom, Netherlands, Hungary, the former German Democratic Republic, Croatia, and Portugal [64, 68]. Recent reports demonstrate that the positive secular decline continues in Denmark [69] and South Korea [70]. Data from Poland illustrate a social gradient and secular change. The mean age at menarche declined somewhat more in girls living in urban conditions than in girls living in towns and villages. Between 1966 and 1978, however, the secular decline was more marked in girls from towns and villages than in urban girls. Subsequently, the mean age at menarche increased from 1978 to 1988; the increase was greatest in girls from towns and least in girls from villages. The recent negative secular trend was probably related to political, social, and economic conditions [71, 72].

Data from longitudinal studies in Europe spanning 50 years and from the United States spanning 75 years provide estimates of age at PHV. In Europe the age at PHV varied between 13.8 and 14.2 years for boys in 25 of 26 samples and between 11.6 and 12.3 years for girls in 24 of 25 samples. In the United States, the age at PHV varied between 11.3 and 11.9 years in girls and between 13.3 and 14.1 years in boys. With allowance for differences in the method of estimating age at PHV, sampling errors, and the uniqueness of the longitudinal samples, these data suggest no clear secular trend [3].

In contrast, data from the annual School Health Surveys conducted in Japan show a gradual decline in maximal increment age (MIA), which is similar but not identical to age at PHV. MIA declined (positive secular change) from the beginning of the twentieth century and subsequently increased (negative secular trend) during World War II and the years immediately thereafter; subsequently, the decline continued through the 1990s. Overall, the estimated rate of the trend has slowed between 1960 and 1990 [73]. Similar changes were observed in Taiwan and in mainland China [3].

Factors that affect secular changes

Many reasons have been postulated for the trend toward earlier maturity, but the underlying causes are not known with certainty. It is reasonable to assume that many interrelated factors are involved, especially the elimination of growth-inhibiting factors. Improved living conditions, sanitation, and overall public health, as reflected in the marked reduction in infant and childhood mortality and morbidity, are primary contributors [49, 64, 74]. Improved nutrition and associated beneficial changes in public health are related factors [3]. Although genetic changes have also been postulated, secular changes occur too rapidly to be accounted for by genetic changes in a population [49, 74]. Decline in family size, increased sexual

* National Center for Health Statistics. Executive summary of the growth chart workshop 1992. Hyattsville, Md, USA: Centers for Disease Control and Prevention, 1994.

stimulation, and decreased "pastoralization" (raising livestock as a primary economic activity) have also been suggested as contributing factors [3, 64].

Recommendations for the construction of an international growth standard for preadolescent and adolescent children

Because biological maturation is closely related to growth, it is of relevance in monitoring the growth status of children and adolescents and also in screening of children at risk. Thus, it is important to include indicators of biological maturation in all growth studies [3, 5, 75].

With allowance for the limitations and advantages of the different indicators of biological maturation considered in this chapter, it is recommended that the following be included: indicators of sexual maturation (stages of pubic hair and breast development and age at menarche in girls, and stages of pubic hair and genital development in boys); indicators of the adolescent growth spurt (age at takeoff and age at PHV); and skeletal maturity. If possible, it would be helpful to have samples of saliva or blood to measure the stable levels of steroid hormones and perhaps IGF-I. Measures of the pulsatile nature of the peptide hormones are entirely impractical and would probably show more variability than the physical measures. Information concerning the state of the hypothalamic–pituitary–gonadal axis, including ovarian cycles, can be obtained from the concentrations of pregnanediol glucuronide, estrone conjugates, and the gonadotropins measured in urine by specific chemiluminescent assays [76].

A cross-sectional design is adequate for the construction of reference data. However, if an accurate description of growth and maturation patterns is desirable, a longitudinal or mixed longitudinal design is required.

In closing, it should be noted that among auxologists opposite views have been expressed with regard to the construction and practicality of a universal growth reference:

> This diversity is important if genetic differences cause growth variations, but a considerable literature indicates differences cause only a minor part of the growth variances between populations. This implies that a single set of reference data could be used internationally if it were obtained by excellent procedures from a *population free of retarding influences* [emphasis added] (Roche [75], p. 80)
>
> In regard to standards for individuals, it used to be said that the growth of all healthy populations, at least up to age five was about the same and one universal standard would do for all. The data in this book make it plain that this is a misconception, based on an inadequate sample of populations…. Clearly what is needed—and what is very actively in progress—is for countries, or at least broad regions, to generate their own standards. These should be based on *well-nourished healthy individuals*, [emphasis added] or the nearest approach to that ideal that is practicable, and if used over adolescence they should be longitudinal and have separate channels for early and late maturers (Eveleth and Tanner [49], p. 15).

The material presented in this volume must provide a sound basis to decide which of these positions is based on sound evidence presently available.

References

1. Beunen G. Physical growth, maturation and performance. In: Eston R, Reilly T, eds. Kinanthropometry and exercise physiology laboratory manual. Vol 1: Anthropometry. Tests, procedures and data. London: Routledge, 2001:65–90.
2. Beunen G, Malina RM. Growth and biological maturation: relevance to athletic performance. In: Bar-Or O, ed. The child and adolescent athlete. Encyclopaedia of sports medicine, vol VI. Oxford, UK: Blackwell, 1996:3–24.
3. Malina RM, Bouchard C, Bar-Or O. Growth, maturation, and physical activity, 2nd ed. Champaign, Ill, USA: Human Kinetics, 2004.
4. Roche AF. Bone growth and maturation. In: Falkner F, Tanner JM, eds. Human growth. Vol 2. Postnatal growth, neurobiology. New York: Plenum, 1986:25–60.
5. Tanner JM. Growth at adolescence, 2nd ed. Oxford, UK: Blackwell, 1962.
6. Acheson RM. Maturation of the skeleton. In: Falkner F, ed. Human development. Philadelphia, Pa, USA: Saunders, 1966:465–502.
7. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist, 2nd ed. Palo Alto, Calif, USA: Stanford University Press, 1959.
8. Todd TW. Atlas of skeletal maturation. St Louis, Mo, USA: Mosby, 1937.
9. Roche AF, Wainer H, Thissen D. Skeletal maturity: the knee joint as a biological indicator. New York: Plenum Press, 1975.
10. Tanner JM, Whitehouse RH, Healy MJR. A new system for estimating skeletal maturity from the hand and wrist, with standards derived from a study of 2,600 healthy British children. Paris: International Children's Centre, 1962.
11. Tanner JM, Whitehouse RH, Marshall WA, Healy MJR, Goldstein H. Assessment of skeletal maturity and prediction of adult height (TW2 method). New York: Academic Press, 1975.
12. Tanner JM, Whitehouse RH, Cameron N, Marshall WA, Healy MJR, Goldstein H. Assessment of skeletal maturity and prediction of adult height. 2nd ed. New York: Academic Press, 1983.

13. Tanner JM, Healy MJR, Goldstein H, Cameron N. Assessment of skeletal maturity and prediction of adult height (TW3 method), 3rd ed. London: Saunders, 2001.
14. Roche AF, Chumlea WC, Thissen D. Assessing the skeletal maturity of the hand-wrist: Fels Method. Springfield, Ill, USA: Charles C Thomas, 1988.
15. Tanner JM, Gibbons RD. A computerized image analysis system for estimating Tanner-Whitehouse 2 bone age. Horm Res 1994;42:282–87.
16. Tanner JM, Oshman D, Lindgren G, Grunbaum JA, Elsouki R, Labarthe D. Reliability and validity of computer-assisted estimates of Tanner-Whitehouse skeletal maturity (CASAS): comparison with the manual method. Horm Res 1994;42:288–94.
17. Roemmich JN, Blizzard RM, Peddada SD, Malina RM, Roche AF, Tanner JM, Rogol AD. Longitudinal assessment of hormonal and physical alterations during normal puberty in boys. IV: Prediction of adult height by the Bailey-Pinneau, Roche-Wainer-Thissen, and Tanner-Whitehouse methods compared. Am J Hum Biol 1997;9:371–80.
18. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Dis Child 1969;44: 291–303.
19. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970;45:13–23.
20. Prader A. Testicular size: assessment and clinical importance. Triangle 1966;7:240–3.
21. Zachmann M, Prader A, Kind HP, Hafliger H, Budliger H. Testicular volume during adolescence. Cross-sectional and longitudinal studies. Helv Paediatr Acta 1974;29:61–72.
22. Fisher DA. Thyroid function in the fetus. In: Fisher DA, Burrow GN, eds. Perinatal thyroid physiology and disease. New York, Raven Press, 1975:21.
23. Underwood LE, D'Ercole AJ. Insulin and insulin-like growth factors/somatomedins in fetal and neonatal development. Clin Endocrinol Metab 1984;13:69–81.
24. MacLaughlin DT, Teixeira J, Donahoe PK. Perspective: reproductive tract development—new discoveries and future directions. Endocrinology 2001;142:2167–72.
25. Winter JS, Faiman C. Pituitary-gonadal relations in male children and adolescents. Pediatr Res 1972;6:126–35.
26. Griffin JE, Wilson JD. Disorders of the testes and the male reproductive tract. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, eds. Williams textbook of endocrinology, 10th ed. Philadelphia, Pa, USA: Saunders, 2003:709–69.
27. Zhang J, Peddada SD, Malina RM, Rogol AD. Longitudinal assessment of hormonal and physical alterations during normal puberty in boys. VI. Modeling of growth velocity, mean growth hormone (GH mean), and serum testosterone (T) concentrations. Am J Hum Biol 2000; 12:814–24.
28. Gasser T, Kohler W, Muller HG, Kneip A, Largo R, Molinari L, Prader A. Velocity and acceleration of height growth using kernel estimation. Ann Hum Biol 1984;11:397–411.
29. Hauspie R, Chrzastek-Spruch H. Growth models: possibilities and limitations. In: Johnston FE, Zemel B, Eveleth PB, eds. Human growth in context. London: Smith-Gordon, 1999:15–24.
30. Marubini E. Mathematical handling of long-term longitudinal data. In: Falkner F, Tanner JM, eds. Human growth. Vol 1. Principles and prenatal growth. New York: Plenum, 1978:209–25.
31. Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. J Pediatr 1952;40:423–41.
32. Roche AF, Wainer H, Thissen D. Predicting adult stature for individuals. Monogr Paediatr 1975;3:1–114.
33. Roche AF, Wainer H, Thissen D. The RWT method for the prediction of adult stature. Pediatrics 1975;56: 1027–33.
34. Khamis HJ, Roche AF. Predicting adult stature without using skeletal age: the Khamis-Roche method. Pediatrics 1994;94(4 Pt 1):504–7. Erratum in: Pediatrics 1995; 95:457.
35. Beunen GP, Malina RM, Lefevre J, Claessens AL, Renson R, Simons J. Prediction of adult stature and noninvasive assessment of biological maturation. Med Sci Sports Exerc 1997;29:225–30.
36. Demirjian A. Dentition. In: Falkner F, Tanner JM, eds. Human growth. Vol 2. Postnatal growth, neurobiology. New York: Plenum, 1986:269–98.
37. Demirjian A, Goldstein H, Tanner JM. A new system of dental age assessment. Hum Biol 1973;45:211–27.
38. Demirjian A, Buschang PH, Tanguay R, Patterson DK. Interrelationships among measures of somatic, skeletal, dental, and sexual maturity. Am J Orthod 1985;88:433–8.
39. Bielicki T, Koniarek J, Malina RM. Interrelationships among certain measures of growth and maturation rate in boys during adolescence. Ann Hum Biol 1984; 11:201–10.
40. Bielicki T. Interrelationships between various measures of maturation rate in girls during adolescence. Studies in Physical Anthropology 1975;1:51–64.
41. Nicolson AB, Hanley C. Indices of physiological maturity: derivation and interrelationships. Child Dev 1953;24:3–38.
42. Malina RM, Bouchard C, Beunen G. Human growth: selected aspects of current research on well nourished children. Annu Rev Anthropol 1988;17:187–219.
43. Beunen G, Malina RM. Growth and physical performance relative to the timing of the adolescent spurt. Exerc Sport Sci Rev 1988;16:503–40.
44. Largo RH, Prader A. Pubertal development in Swiss boys. Helv Paediatr Acta 1983;38:211–28.
45. Largo RH, Prader A. Pubertal development in Swiss girls. Helv Paediatr Acta 1983;38:229–43.
46. Thomis MA, Towne B. Genetic determinants of prepubertal and pubertal growth and development. Food Nutr Bull 2006;27(suppl):S257–78.
47. Pena Reyes RM, Malina RM. Fels and Tanner-Whitehouse skeletal ages of school children 7–13 years in Oaxaca, Mexico. In: Dasgupta P, Hauspie R eds. Perspectives in human growth, development and maturation. Dordecht, Netherlands: Kluwer Academic Publishers, 2001:55–65.
48. Cameron N, Wright CA. The start of breast development and age at menarche in South African black females. S Afr Med J 1990;78:536–9.
49. Eveleth PB, Tanner JM. Worldwide variation in human growth. 2nd ed. Cambridge, UK: Cambridge University Press, 1990.
50. Gillett-Netting R, Meloy M, Campbell BC. Catch-up

reproductive maturation in rural Tonga girls, Zambia? Am J Hum Biol 2004;16:658–69.
51. Kimura K. Studies on growth and development in Japan. Yearb Phys Anthropol 1984;27:179–214.
52. Murata M. Population-specific reference values for bone age. Acta Paediatr Suppl 1987;423:113–4.
53. Loucks AB. Energy availability, not body fatness, regulates reproductive function in women. Exerc Sport Sci Rev 2003;31:144–8.
54. Garn SM, LaVelle M, Rosenberg KR, Hauthorne VM. Maturational timing as a factor in female fatness and obesity. Am J Clin Nutr 1986;43:879–83.
55. Padez C. Social background and age at menarche in Portuguese university students: a note on the secular changes in Portugal. Am J Hum Biol 2003;15:415–27.
56. Malina RM, Katzmarzyk PT, Bonci CM, Ryan RC, Wellens RE. Family size and age at menarche in athletes. Med Sci Sports Exerc 1997;29:99–106.
57. Roberts DF. Climate and human variability. Module in anthropology no. 34. Reading, Mass, USA: Addison-Wesley, 1973.
58. Marshall WA. Evaluation of growth rate in height over periods of less than one year. Arch Dis Child 1971;46:414–20.
59. Reynolds EL, Sontag LW. Seasonal variation in weight, height and appearance of ossification centers. J Pediatr 1944;24:524–35.
60. Mirwald RL, Bailey DA. Seasonal height velocity variation in boys and girls 8–18 years. Am J Hum Biol 1997; 9:709–15.
61. Goldstein H. The design and analysis of longitudinal studies. London: Academic Press, 1979.
62. Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, Hasemeier CM. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings Network. Pediatrics 1997;99:505–12.
63. Cole TJ. The International Growth Standard for Preadolescent and Adolescent Children: Statistical considerations. Food Nutr Bull 2006;27(suppl):S237-243.
64. Danker-Hopfe H. Menarcheal age in Europe. Yearb Phys Anthropol 1986;29:81–112.
65. Brundtland GH, Walloe L. Menarcheal age in Norway in the 19th century: a re-evaluation of the historical sources. Ann Hum Biol 1976;3:363–74.
66. Liestol K, Rosenberg M. Height, weight and menarcheal age of schoolgirls in Oslo—an update. Ann Hum Biol 1995;22:199–205.
67. Wyshak G, Frisch RE. Evidence for a secular trend in age of menarche. N Engl J Med 1982;306:1033–5.
68. Bodzsar EB, Susanne C, eds. Secular growth changes in Europe. Budapest, Hungary: Eotvos Lorand University Press, 1998.
69. Olesen AW, Jeune B, Boldsen JL. A continuous decline in menarcheal age in Denmark. Ann Hum Biol 2000; 27:377–86.
70. Hwang J-Y, Shin C, Frongillo EA, Shin KR, Jo I. Secular trend in age at menarche for South Korean women born between 1920 and 1986: the Ansan study. Ann Hum Biol 2003;30:434–42.
71. Bielicki T. Secular trends in growth: human biologists' contribution to the study of social change. In: Johnston FE, Zemel B, Eveleth PB, eds. Human growth in context. London: Smith-Gordon, 1999:303–11.
72. Bielicki T, Hulanicka B. Secular trend in stature and age at menarche in Poland. In: Bodzsar EB, Susanne C, eds. Secular growth changes in Europe. Budapest, Hungary: Eotvos Lorand University Press, 1998:263–79.
73. Ali MA, Ohtsuki F. Estimation of maximum increment age in height and weight during adolescence and the effect of World War II. Am J Hum Biol 2000;12:363–70.
74. Malina RM. Secular changes in size and maturity: causes and effects. Monogr Soc Res Child Dev 1979;44(179):59–102.
75. Roche AF. Growth, maturation and body composition. The Fels Longitudinal Study 1929–1991. Cambridge, UK: Cambridge University Press, 1992.
76. Santoro N, Crawford SL, Allsworth JE, Gold EB, Greendale GA, Korenman S, Lasley BL, McConnell D, McGaffigan P, Midgely R, Schocken M, Sowers M, Weiss G. Assessing menstrual cycles with urinary hormone assays. Am J Physiol Endocrinol Metab 2003;284: E521–30.