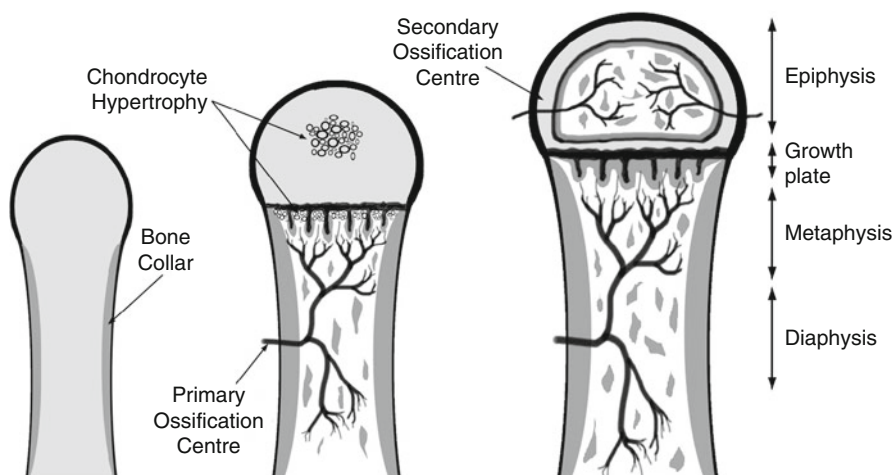


Skeletal maturity is a measure of development incorporating the size, shape and degree of mineralization of bone to define its proximity to full maturity. The assessment of skeletal maturity involves a rigorous examination of multiple factors and a fundamental knowledge of the various processes by which bone develops.

Longitudinal growth in the long bones of the extremities occurs through the process of endochondral ossification. In contrast, the width of the bones increases by development of skeletal tissue directly from fibrous membrane. The latter is the mechanism by which ossification of the calvarium, the flat bones of the pelvis, the scapulae, and the body of the mandible occurs. Initial calcification begins near the center of the shaft of long bones in a region called the primary ossification center [1].

Although many flat bones, including the carpal bones, ossify entirely from this primary center, all of the long bones develop secondary centers that appear in the cartilage of the extremities of the bone. Maturation in these centers proceeds in a manner identical to that in the primary centers with ossification of cartilage and invasion of osteoclasts and osteoblasts. The bone ossified from the primary center is the diaphysis, while the bone ossified from the secondary center is the epiphysis. As the secondary center is progressively ossified, the cartilage is replaced by bone until only a thin layer of cartilage, the epiphyseal plate, separates the diaphyseal bone from the epiphysis. The part of the diaphysis that abuts on the epiphysis is referred to as the metaphysis and represents the growing end of the bone. As long as the epiphyseal cartilage plate persists, both the diaphysis and epiphysis continue to grow, but, eventually, the osteoblasts cease to multiply and the epiphyseal plate is ossified. At that time, the osseous structures of the diaphysis and epiphysis are fused and growth ceases [1] (Fig. 2.1).

In the fetal phase of life, the principle interest in skeletal growth is associated with the diagnosis of prematurity. The end of the embryonic period and the beginning of the fetus is marked by the event of calcification, which begins at 8 or 9 weeks. By the 13th fetal week, most primary centers of the tubular bones are well-developed into diaphyses, and, at birth, all diaphyses are completely ossified, while most of the epiphyses are still cartilaginous. Ossification of the distal femoral epiphysis



**Fig. 2.1** Schematic representation of endochondral bone formation. Skeletal maturity is mainly assessed by the degree of development and ossification of the secondary ossification centers in the epiphysis

begins during the last 2 months of gestation, and this secondary center is present in most full term babies. Similarly, the ossification center for the proximal epiphysis of the humerus usually appears about the 40th week of gestation. On the other hand, the centers for the proximal epiphyses of the femur and tibia may not be present in full term infants, but appear in the first few months of life [2, 3].

After birth, the epiphyses gradually ossify in a largely predictable order, and, at skeletal maturity, fuse with the main body of the bone. Comparing the degree of maturation of the epiphyses to normal age-related standards forms the basis for the assessment of skeletal maturity, the measure of which is commonly called “bone age” or “skeletal age”. It is not clear which factors determine a normal maturational pattern, but it is certain that genetics, environmental factors, and hormones, such as thyroxine, growth hormone, and sex steroids, play important roles. Studies in patients with mutations of the gene for the estrogen receptor or for aromatase enzyme have demonstrated that it is estrogen that is primarily responsible for ultimate epiphyseal fusion, although it seems unlikely that estrogen alone is responsible for all skeletal maturation [4].

## Clinical Applications for Skeletal Determinations

A single reading of skeletal age informs the clinician of the relative maturity of a patient at a particular time in his or her life, and, integrated with other clinical findings, separates the normal from the relatively advanced or retarded. Successive skeletal age readings indicate the direction of the child’s development and/or show his or her progress under treatment. In normal subjects, bone age should be roughly

within 10% of the chronological age. Greater discordance between skeletal age and chronological age occurs in children who are obese or who start puberty early, as their skeletal age is accelerated.

There are two main applications for evaluations of skeletal maturation: the diagnosis of growth disorders and the prediction of final adult height.

## Diagnosis of Growth Disorders

Assessments of skeletal age are of great importance for the diagnosis of growth disorders, which may be classified into two broad categories with different etiologies, prognoses and treatments. Primary growth deficiency is due to an intrinsic defect in the skeletal system, such as bone dysplasia, resulting from either a genetic defect or prenatal damage and leading to shortening of the diaphysis without significant delay of epiphyseal maturation. Hence, in this form of growth disorder, the potential normal bone growth (and therefore, body growth) is impaired, while skeletal age is not delayed or is delayed much less than is height.

Secondary growth deficiency is related to factors, generally outside the skeletal system, that impair epiphyseal or osseous maturation. These factors may be nutritional, metabolic, or unknown, as in the syndrome of idiopathic (constitutional) growth delay. In this form of growth retardation, skeletal age and height may be delayed to nearly the same degree, but, with treatment, the potential exists for reaching normal adult height.

The distinction between these categories may be difficult in some instances in which skeletal age is delayed to a lesser degree than height. In general, however, differentiation between primary and secondary categories of growth failure can be determined from clinical findings and skeletal age [5].

## Final Height Predictions

The adult height of a child who grows up under favorable environmental circumstances is, to a large extent, dependent on heredity. The final height of the child may, therefore, be postulated from parental heights. Indeed, various methods of final height predictions, which take into account parental height, have been described [6]. A child's adult height can also be predicted from his or her heights at earlier ages, with correlations on the order of 0.8. However, children differ greatly in rate of development; some attain maturity at a relatively early age, while others have a slow tempo and finish growing relatively late. Hence, knowledge of the degree of development increases the accuracy of final height predictions. The only practical guide to acquire this knowledge is by assessment of skeletal maturity, usually estimated from a hand and wrist radiograph.

Tables for prediction of ultimate height based on the individual's height, skeletal age, sex, age, and growth rate have been published. Using skeletal age for prediction of ultimate height, it is also possible to make a rough calculation as follows: measure

the individual's height, plot it on a standard growth curve, and extrapolate the value horizontally to the age on the chart that is equal to the bone age. If the point of extrapolation falls between the 5th and 95th centiles, then a guarded prediction of normal adult stature can be given. The closer the extrapolated value is to the 50th centile, the more accurate it is likely to be [5].

Other bone age and height prediction methods commonly in use are those of Bayley-Pinneau, Roche et al. and Tanner-Whitehouse [7–9]. All of these methods use radiographs of the hand and wrist to assess skeletal maturity and were based on population data from normal children followed to adult height. Overall, these methods have 95% confidence intervals of 7–9 cm when used to predict the final height of individuals. It is necessary to realize, however, that estimations of final height are most accurate in children who are healthy, and, in the sick, these predictions are less reliable.

Below is the formula for the prediction of adult height estimated by J.M. Tanner et al. [9]:

$$\begin{aligned} \text{Predicted Final Height} = & \text{Height Coefficient} \times \text{Present Height (cm)} + \\ & \text{Age Coefficient} \times \text{Chronological Age (years)} + \\ & \text{Bone Age Coefficient} \times \text{Bone Age (years)} + \\ & \text{Constant} \end{aligned}$$

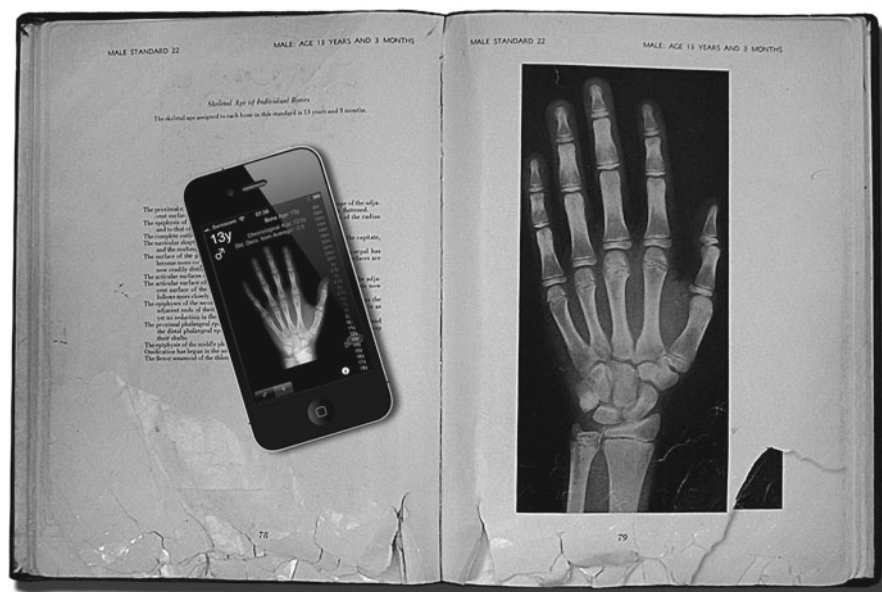
In girls, these investigators incorporated knowledge of whether or not menarche had occurred, which improved their predictions. The tables for the coefficients for prediction of adult height are on pages 93 and 94.

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## Conventional Techniques for Skeletal Determinations

In the evaluation of physical development in children, variations in maturation rate are poorly described by chronological age. Thus, for many decades, scientists have sought better techniques to assess the degree of development from birth to full maturity. Measures of height, weight, and body mass, although closely related to biological maturation, are not sufficiently accurate due to the wide variations in body size. Similarly, the large variations in dental development have prevented the use of dental age as an overall measure of maturation, and other clinically established techniques are of limited value. As examples, the age at menarche, although an important biological indicator, relates to only half the population, and determinations of sexual development using the Tanner classification, while an extremely useful clinical tool, is subjective and restricted to the adolescent period. Unfortunately, most available maturational “age” scales have specific uses and tempos that do not necessarily coincide.

Skeletal age, or bone age, the most common measure for biological maturation of the growing human, derives from the examination of successive stages of skeletal development, as viewed in hand-wrist radiographs. This technique, used by pediatricians, orthopedic surgeons, physical anthropologists and all those interested in the study of human growth, is currently the only available indicator of



**Fig. 2.2** Comparison of the traditional Greulich and Pyle atlas used for determination of bone maturity from hand radiographs and the electronic alternative, a digital atlas of “idealized” hand radiographs that can be reviewed on standard hand-held PDAs

development that spans the entire growth period, from birth to maturity. Essentially, the degree of skeletal maturity depends on two features: growth of the area undergoing ossification, and deposition of calcium in that area. While these two traits may not keep pace with each other, nor are they always present concurrently, they follow a fairly definite pattern and time schedule, from infancy to adulthood. Through radiographs, this process provides a valuable criterion for estimating normal and abnormal growth and maturation (Fig. 2.2).

Greulich and Pyle and Tanner-Whitehouse (TW2) are the most prevalently employed skeletal age techniques today [10, 11]. Despite their differing theoretical approaches, both are based on the recognition of maturity indicators, i.e., changes in the radiographic appearance of the epiphyses of tubular bones from the earliest stages of ossification until fusion with the diaphysis, or changes in flat bones until attainment of adult shape [12].

The standards established by Greulich and Pyle, undoubtedly the most popular method, consist of two series of standard plates obtained from hand-wrist radiographs of white, upper middle-class boys and girls enrolled in the Brush Foundation Growth Study from 1931 to 1942. Represented in the Greulich and Pyle atlas are ‘central tendencies’, which are modal levels of maturity within chronological age groups. The skeletal age assigned to each standard corresponds to the age of the children on whom the standard was based. When using the Greulich and Pyle method, the radiograph to be assessed is compared with the series of standard plates, and the age given to the standard plate that fits most closely is assigned as the

skeletal age of the child. It is often convenient to interpolate between two standards to assign a suitable age to a radiograph. The apparent simplicity and speed with which a skeletal age can be assigned has made this atlas the most commonly used standard of reference for skeletal maturation worldwide.

Underlying the construction of the Greulich and Pyle atlas are the assumptions that, in healthy children, skeletal maturation is uniform, that all bones have an identical skeletal age, and that the appearance and subsequent development of body centers follow a fixed pattern. However, considerable evidence suggests that a wide range of normal variation exists in the pattern of ossification of the different bones of the hand and the wrist and that this variation is genetically determined. In fact, most standards in the atlas include bones that differ considerably in their levels of maturity [10].

Greulich and Pyle did not formally recommend any specific technique for the use of their atlas. Rather, they suggested that atlas users develop their own method depending on their preferences. Pyle et al. did, however, suggest the rather cumbersome approach that each ossification center be assigned a bone-specific bone age, and the average of the ages calculated. By and large, when there is a discrepancy between the carpal bones and the distal centers, greater weight should be assigned to the distal centers because they tend to correlate better with growth potential [5].

A number of important caveats concerning bone age must be considered. First, experience in skeletal maturity determinations and a similar analytic approach are essential to enhance inter- and intra-observer reproducibility. Clinical studies and trials involving bone age as an outcome measure greatly benefit from the inclusion of experienced readers who use similar approaches in their assessments. Second, the normal rate of skeletal maturation differs between males and females, and ethnic variability exists. Lastly, these references are not necessarily applicable to children with skeletal dysplasias, endocrine abnormalities or a variety of other causes of growth retardation.

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## Computer Assisted Techniques for Skeletal Determinations

With the advent of digital imaging, several investigators have attempted to provide an objective computer-assisted measure for bone age determinations and have developed image processing techniques from reference databases of normal children that automatically extract key features of hand radiographs [13–17]. To date, however, attempts to develop automated image analysis techniques capable of extracting quantitative measures of the morphological traits depicting skeletal maturity have been hindered by the inability to account for the great variability in development and ossification of the multiple bones in the hand and wrist. In an attempt to overcome these difficulties, automated techniques are being developed that primarily rely on measures of a few ossification centers, such as those of the epiphyses.

In the design of this digital atlas, the complexities associated with the design of software that integrates all morphological parameters was circumvented through the selection of an alternative approach. We designed artificial, idealized, sex- and age-specific images of skeletal development that incorporated the different degrees of

maturation of each ossification center in the hand and wrist. The idealized image was derived from a composite of several hand radiographs from healthy children and adolescents that were identified as the perfect average for each ossification center in each age group.

Our aim was to provide a portable alternative to the reference books currently available, while avoiding the complexity of computer assisted image analysis. The wide adoption of personal digital assistants (PDAs) and pocket computer devices allowed the implementation of a low-cost portable solution that could effectively replace the traditional reference books. Technical challenges included the development of proper compression and image enhancement techniques for interpretation of hand radiographs on a small screen with adequate quality, and the need to store a large number of images on instruments with limited memory capacity.

Hand Bone Age

A Digital Atlas of Skeletal Maturity

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