Bone Age: A Handy Tool for Pediatric Providers

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abstract

Pediatricians have relied on methods for determining skeletal maturation for >75 years. Bone age continues to be a valuable tool in assessing children's health. New technology for bone age determination includes computer-automated readings and assessments obtained from alternative imaging modalities. In addition, new nonclinical bone age applications are evolving, particularly pertaining to immigration and children's rights to asylum. Given the significant implications when bone ages are used in high-stake decisions, it is necessary to recognize recently described limitations in predicting accurate age in various ethnicities and diseases. Current methods of assessing skeletal maturation are derived from primarily white populations. In modern studies, researchers have explored the accuracy of bone age across various ethnicities in the United States. Researchers suggest there is evidence that indicates the bone ages obtained from current methods are less generalizable to children of other ethnicities, particularly children with African and certain Asian backgrounds. Many of the contemporary methods of bone age determination may be calibrated to individual populations and hold promise to perform better in a wider range of ethnicities, but more data are needed.

Bone age is an interpretation of skeletal maturity, typically based on radiographs of the left hand and wrist or knee, that has provided useful information in various clinical settings for >75 years. A child's bone age may or may not approximate his or her chronologic age (the actual age of the child in years according to his or her birth date). Many factors influence the progression of skeletal development, including nutrition, genetics, hormones, and disease states. Although many providers routinely order a bone age study when evaluating growth, the test can provide useful information for many clinical concerns.

Pediatricians need to be aware that assessments of skeletal maturity now have wider applications, ranging from elite sports selection and forensics to international immigration programs. For example, many children seeking asylum are required to undergo a bone age study, which may determine placement and access to resources.

Given its importance when bone age is used in high-stake decisions (such as immigration or legal matters), its limitations must be recognized in predicting accurate age in various ethnicities and disease states. Bone age is an old test, but new data reveal how the standardized methods compare with each other and perform for various ethnicities. Additionally, alternate methods for determining bone age are being pioneered, including automated methods, ultrasonography, and MRI. With this present review, we aim to identify the expected maturation changes in various disease states, explore recent clinical and nonclinical applications of bone age, summarize limitations in methods of skeletal maturity assessments, and discuss upcoming technology.

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STATE-OF-THE-ART REVIEW ARTICLE

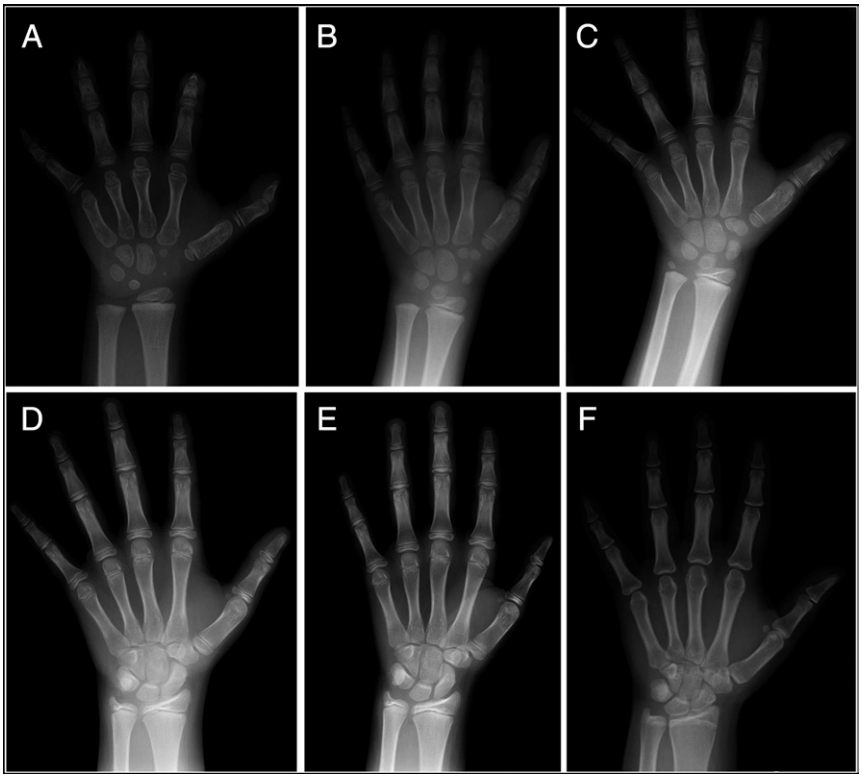

FIGURE 1
An example of skeletal maturation during childhood at various ages. A, 5 years of age. B, 7 years of age. C, 9 years of age. D, 11 years of age. E, 13 years of age. F, 15 years of age.

METHODS OF ASSESSING SKELETAL MATURITY

The basis for skeletal maturation assessment lies in the predictable changes of ossification centers over time (Fig 1). Long bones, including the ulna, radius, and phalanges, grow until the ends of the bones (epiphyses) fuse with the metaphyses at the growth plates. This growth plate fusion does not happen at the same time uniformly in a child's body.[1] The radiograph of the hand in particular reveals many ossification centers, with progression over time, and it is the standard for estimating bone ages in children older than 3 years of age (Fig 1). Children and infants younger than 3 years of age have changes in the knee that can be more easily appreciated and compared with changes in the hand; therefore, radiographs of the knee or even the hemiskeleton are often used for young children.[2]

Standardized methods of scoring skeletal maturity have existed for almost 100 years. The 2 most commonly used methods are the Tanner-Whitehouse (TW) and Greulich-Pyle (GP) methods.[3–6] The TW method was initially developed in the 1930s with white European children.[4] The Tanner-Whitehouse, second edition (TW2), based on data from the 1950s and 1960s, was published in 1983 and updated in 2001 as the Tanner-Whitehouse, third edition (TW3).[5,6] The TW3 method estimates ages that are slightly younger than estimates with the TW2 method.[7] The TW method calculates a radius, ulna, and short bones score, with each major bone in the hand contributing to the total score. A meta-analysis deemed TW3 a more accurate estimate of age than TW2 or GP in white populations, and both TW3 and TW2 were more accurate than GP in white children.[8] The TW method, estimated to take 7.9 minutes, is the preferred method among European endocrinologists.[9,10]

The GP method is most commonly used by pediatric radiologists and endocrinologists in the United States. First published in 1950 and revised in 1988, it is based on 1000 radiographs of children in Cleveland, Ohio.[3] The GP method compares the overall visual appearance of the hand with age standards. This method's disadvantage is that established standards do not exist for weighting different bones (eg, long bones versus carpals), and no hand fits perfectly to 1 standard, so the reviewer must decide which point of maturation dominates. The method is faster (estimated to take 1.4 minutes)[9] and can be taught easily, so that new learners quickly achieve accuracy and their intraobserver variation is comparable to that of an experienced reader.[11] Because it is simpler and quicker, the GP method is preferred by 76% of pediatric endocrinologists and radiologists for determining bone age.[9]

Multiple comparisons have been made in accurately predicting bone age with both methods. In a study of 362 bone age assessments, the 95% confidence interval (CI) for the GP method was −2.46 to 2.18 years; for the TW2 method, it was smaller (95 % CI, 1.42 to 1.43 years).[12] In an Italian sample, chronologic age was more closely approximated with the TW3 method than with the GP and TW2 methods.[13] The GP method scored children consistently younger than the TW2 method, but TW3 age estimates are known to be younger than TW2 estimates.[7,14] In addition, the TW3 method was found to slightly overestimate age, whereas the GP method slightly underestimated age, but the authors of that study concluded that GP was superior because it took less than half the time compared to TW3.[15]

DELAYED BONE AGE

A traditional use of bone age has been to assess a child's growth and future height potential, particularly when a patient presents with concerns about short stature or poor growth. Although many processes result in a delayed bone age (Table 1), constitutional delay (late bloomer) is 1 of the most common causes of a bone age delay and short stature.[16] The conventional definition of constitutional delay is a bone age at least 2 years less than chronologic age in combination with associated short stature, delayed puberty, or reaching final adult height later than peers.[17,18] In contrast, children with familial short stature are short because they have short parents; the children have a normal bone age and are destined to be short like their parents. Many children evaluated at a referral center for short stature have familial short stature in combination with coexisting constitutional delay.[17,18] Although many methods exist to predict adult height, caution is required in making these predictions. Among children with a 4-year delayed bone age, final adult height has been overestimated by 8 cm.[19] Conversely, in children with idiopathic short stature and normal bone age, final adult height predictions have been underestimated.[20] Overall, final adult height predictions have been slightly more accurate for girls than for boys.[19] Serial bone ages and accurate height measurements over time are recommended for continually assessing progress when growth is a concern.

Children with chronic diseases may have a delayed bone age because of the disease process, whereas others have normal skeletal maturation. Children who are born prematurely may have long-standing skeletal maturation delays, and bone age may continue to be slightly delayed until the child is 8 years old.[21] Children with cancer or cardiac, liver, or kidney disease potentially have delays in skeletal maturation.[22–26] Diseases causing nutrient malabsorption, such as inflammatory bowel disease, celiac disease, and cystic fibrosis, are associated with delayed bone age.[27–30] Processes involving active inflammation or infection, such as severe atopic dermatitis, juvenile idiopathic arthritis, and immunodeficiency, can delay bone maturation independently of the poor weight gain that often occurs in children with these conditions.[31–37] Psychiatric disease, such as anorexia and depression, and social circumstances involving neglect and abuse are associated with poor growth and sometimes with delayed skeletal maturation.[38] Poor nutrition or poor nutrition in the context of disease may halt skeletal maturation.[39,40] In addition, delays in skeletal maturation occur in some unique genetic disorders, including trisomy 21 syndrome, Turner syndrome, and Russell-Silver syndrome.[9,16,41–43]

Endocrine problems causing short stature are commonly associated with delayed bone age; thus, a normal bone age is helpful in ruling out many endocrine conditions and further testing.[16] For example, children with severe hypothyroidism do not have normal bone maturation, and the presence of age-appropriate linear growth and a normal bone age are reassuring in the context of thyroid problems. At the extremes, providers must be aware that

TABLE 1 Considerations in Delayed Bone Age

Endocrine
Constitutional delay (late bloomer)
Hypothyroidism
Growth hormone deficiency
Panhypopituitarism
Hypogonadism
Cushing disease
Nutritional
Malnutrition
Failure to gain wt as a result of disease
Inadequate bone mineralization
Medications
Glucocorticoids (including high-dose inhaled corticosteroids and oral budesonide in sensitive children)
Amphetamine and dextroamphetamine (modest effect)
GnRH analogues (depot leuprolide and histrelin)
Aromatase inhibitors
Nonendocrine chronic disease
Congenital heart disease
Chronic kidney disease
Juvenile idiopathic arthritis
Inflammatory bowel disease
Liver disease
Celiac disease
Cystic fibrosis
Severe asthma (likely from corticosteroid use)
Immunodeficiency states, including HIV infection
Active tuberculosis
Female athlete triad (leading to hypogonadism)
Anorexia
Neglect and abuse
Syndromes
Trisomy 13, 18, and 21 syndromes
Turner syndrome
Klinefelter syndrome
Russell-Silver syndrome

GnRH, gonadotropin-releasing hormone.

severe hypothyroidism causes such excessive production of thyrotropin-releasing hormone that crossover stimulation of follicle-stimulating hormone and luteinizing hormone leads to the unusual clinical picture of precocious puberty with delayed bone age.[44]

Long-standing, untreated growth hormone deficiency also leads to delayed skeletal maturation. Central pituitary problems because of malformations, tumors, or infiltrative diseases may also cause delayed bone age from growth hormone deficiency or secondary hypothyroidism from lack of thyrotropin secretion.[45] Also, any cause of hypogonadism at puberty commonly slows skeletal maturation because estrogen and pubertal development are critical in bone maturation. Excess corticosteroid use was thought to oppose skeletal maturation such that Cushing disease (with delayed bone age) could be distinguished from simple obesity (with advanced bone age). However, researchers have reported conflicting evidence of delay, with data from the largest study revealing that Cushing disease was usually associated with normal or advanced bone age, and that only 3% of children with Cushing disease had delayed bone age.[46–49]

Certain medications alter bone development. Most commonly, exogenous corticosteroids may or may not inhibit bone maturation. Small doses of exogenous corticosteroids and even inhaled corticosteroids and oral budesonide are absorbed systemically and may lead to delayed skeletal maturation in select sensitive children.[50–53] Amphetamines and dextroamphetamines, when used to treat attention-deficit/hyperactivity disorder, may decrease height velocity and presumably delay bone age. However, in a prospective study, no maturation delay was found in children taking stimulant medications.[54,55]

TABLE 2 Considerations in Advanced Bone Age

Endocrine
Constitutional advancement (early bloomer)
Hyperthyroidism
Precocious puberty
Premature adrenarche
Ovarian tumors
Leydig cell tumors
Germ cell tumors
Testicular tumors
Brain tumors and malformations (leading to precocious puberty)
Nutritional
Obesity
Medications and supplements
Estrogen
Oral contraceptives
Testosterone preparations
Lavender (estrogen-like effect)
Tea tree oil (estrogen-like effect)
Syndromes
Familial male-limited precocious puberty
McCune-Albright syndrome
Sotos syndrome
Beckwith-Wiedemann syndrome

ADVANCED BONE AGE

A bone age that is rapidly advancing may be a normal variant or a cause for concern (Table 2). As in families with a tendency toward constitutional delay, constitutional advancement (early bloomers) also runs in families.[56] Many families have a history of early puberty. In general, African American girls have earlier puberty and therefore have more relative skeletal advancement when compared with white girls.[57] Although puberty in white children rarely occurs before age 8 years in girls and 9 years in boys, Hispanic and African American girls may have normal puberty as early as 6 years.[58]

Most other causes of bone age advancement are because of sex steroid exposure or obesity. Conditions that accelerate puberty also accelerate bone age advancement. In evaluating precocious pubertal disorders, the presence of a rapidly progressing bone age is concerning. Pathologic causes of precocious puberty that produce enough estrogen, testosterone, or adrenal hormones can cause marked skeletal advancement. Ovarian, Leydig, or germ cell tumors can trigger precocious puberty and lead to rapid skeletal changes. Brain tumors and malformations may also trigger central precocious puberty with skeletal advancement. Adrenal tumors and adrenal disease alone (eg, congenital adrenal hyperplasia) are associated with advanced bone age.[59–63] In addition, hyperthyroidism is associated with an advanced bone age, which may be independent of pubertal progression.[64,65]

Like the process of puberty, medications and supplements with sex steroid effects advance the bone age. Estrogen and oral contraceptive pills, which quickly close epiphyseal plates and halt further growth, are used in growth attenuation therapy as discussed below. Exposure to topical testosterone and estrogen products may also close epiphyseal plates. Less recognized are supplements with potent estrogen effects. Two essential oils, lavender and tea tree oil, may have some estrogen effect when used topically, but the findings have been reported from only small case series.[66,67] Additionally, excessive consumption of foods containing phytoestrogens

(eg, soy) could theoretically advance the bone age, but this possibility has not been studied extensively and remains controversial as an endocrine disrupter.[68,69]

The largest cause of widespread skeletal advancement is the increased prevalence of childhood obesity. Overnutrition is clearly associated with mildly advanced bone age.[70,71] Although these children are typically taller than peers throughout early childhood, many start puberty earlier and their growth plates fuse sooner. The specific mechanism is not well understood, but 2 groups have found correlation between higher homeostatic model assessment of insulin resistance, insulin levels, and bone age advancement, although this may simply reflect higher adiposity and not a causal relationship.[70,72] Many clinicians consider hypothyroidism in the differential diagnosis of severe obesity, but an advanced bone age is unlikely with severe hypothyroidism.

Few syndromes are associated with advanced bone ages. Boys with familial male-limited precocious puberty because of Leydig cell hyperplasia and increased testosterone production have advanced bone ages. Patients with McCune-Albright syndrome are prone to have precocious puberty and hyperthyroidism, resulting in an advanced bone age. Two other overgrowth syndromes, Sotos and Beckwith-Wiedemann syndromes, may accelerate skeletal maturation.[73,74]

Achieving an advanced bone age is an important outcome in growth attenuation therapy. Growth attenuation therapy has historically been offered to tall girls in specific European countries, but it has become less popular because of concerns about future fertility.[75–77] For these girls, ethinyl estradiol is used to achieve rapid bone age advancement and shorter adult height. Applying the same technique to a different population, centers across the United States are offering growth attenuation therapy for developmentally delayed children who will be dependent on caregivers for life, with the hope of improving the child's and parent's quality of life.[78,79]

OTHER BONE AGE APPLICATIONS

Bone age has been used in nonclinical settings. With the emphasis on athletics and athletic performance, bone ages are being used to help guide sporting decisions and resources for potentially elite athletes. Young boy athletes who want to participate competitively in sports that emphasize stature may have bone age assessments to decide how much time and how many resources to invest in early sport-specific training.[80] For 477 young, white boy athletes who presented to an outpatient sports medicine clinic and requested estimates for final adult height, results from the TW2 method for estimating adult heights agreed with the final adult heights achieved.[80] In addition, bone age, along with a pubertal timing estimate, can predict success for early-maturing boys in most sports and for late-maturing girls in gymnastics and ballet.[81]

Although official recommendations are against using bone age to determine age when age is unknown, bone age is still used in both legal and policy matters.[82] In forensic cases, the TW3 method has been deemed most accurate.[83] Another application that pediatric providers must be aware of is the use of bone age to accept or deny international immigration. The United Nations Convention on the Rights of the Child gives children the right to universal safeguards and concessions.[84] With more children and adolescents crossing borders, being separated from families, and not having documentary evidence of age, many countries must decide how to grant asylum and provide protection and welfare as fairly as possible.[85] The US Immigration and Customs Enforcement suggests that age examination based on wrist and hand radiographs may be considered, but they should not be used as complete evidence.[86] Although each country has a variation of the process, the assessment of skeletal maturity by bone age for age determination is the second most common technique after interview or documentation.[85]

The United Nations High Commissioner for Refugees guidelines suggest accounting for the child's physical maturation and psychological maturation.[87] Other organizations, such as the United Nations Children's Fund, highlight the importance of the cultural and social context of age assessments and interpretation of skeletal assessments.[88] Although some countries rely heavily on bone age, others consider the entire developmental picture, supported by experts who encourage a more global and flexible approach.[89–91] In some sources, researchers suggest that combinations of skeletal and dental age assessments, still limited by ethnic variations, may improve accuracy for immigration purposes.[92–95] Sweden, a country that admits some of the largest numbers of unaccompanied children in Europe (35 000 children in 2015 alone), began a new system in 2017 that includes dental and skeletal assessments to determine age.[96]

LIMITATIONS IN BONE AGE DETERMINATION

With potentially important decisions resting on the accuracy of determining bone age, the shortcomings of the various methods for assessing skeletal maturity must be understood. Both TW and GP methods developed standards based on a largely white population. An

early comparison of 599 bone ages across various ethnicities found the most discrepancies among African American girls and boys, Hispanic girls, and Asian American boys.[97] The GP method was assessed blindly by radiologists who read films of children from 4 ethnic backgrounds living in Los Angeles from 2003 to 2013.[98] When compared to GP standards, Asian American boys showed a significant characteristic delay in bone age from ages 2 to 7 years (P = .03), and children aged 4 to 6 years had a delay of >2 years. Data for African Americans did not reveal a tight correlation with GP standards; many values were outside the normal limits, with significantly advanced and delayed bone ages (P = .048). The GP standards did reveal close congruence between Hispanic and white children.[98] In another assessment, values for African American children were shown to have significantly advanced bone ages compared to GP standards (P = .002); values for 10% of the children were outside 2 SDs.[99]

As providers care for children of various ethnicities, results from international studies may be increasingly relevant (Table 3). Indonesian girls had an estimated 0.5-year delay in bone age compared with white girls, and Indonesian boys had a 1-year delay compared with white boys.[100] Korean children's bone ages were accurately estimated with both GP and TW3 methods, and both showed good correlation with chronologic age.[101] Indian children also had delayed bone age, with up to a 1-year delay in boys aged 7 to 12 years.[102] In Pakistan, researchers in 1 study found that the GP method results correlated closely with age for girls but not for boys,[103] and in a larger study, researchers found that chronologic age compared with bone age for boys and girls when the GP method was used.[104] In a large-scale evaluation of Iranian children, researchers concluded that bone age for boys was 4.5 months less than GP standards, and bone age for girls was older by 0.5 months compared to GP standards.[105] In Italy, the TW2, TW3, and GP methods were compared among patients aged 6 to 20 years. The TW2 method had errors for both sexes and was deemed unreliable; the GP and TW3 methods predicted age among boys equally well, but among girls the TW3 method was superior to GP.[13] In a Scottish study, researchers found good correlation between the GP method and the study population, with a slight tendency to overestimate the ages of girls and underestimate the ages of boys younger than 13 years.[106]

TABLE 3 Ethnic Variations in Skeletal Maturation Compared With White Children

Delayed
Middle Eastern boys: 0.25–0.5-y delay
Pakistani boys: 0.5-y delay
Iranian boys: 0.5-y delay
Southeast Asian children
Average delay: 0.5 y
Indonesian boys: 1-y delay
Indonesian girls: 0.5-y delay
Indian children: 1-y delay (boys > girls)
Asian American boys
Children <7 y old: ≥2-y delay
Advanced
African American children, especially girls: markedly advanced (10% are >2 SDs advanced)
Middle Eastern girls
Iranian girls
No change
Korean children
Pakistani girls
Italian children
Scottish children

TECHNOLOGY AND FUTURE DIRECTIONS

New commercial means are available for automating the bone age reading and for determining bone age from other imaging modalities. In 2008, the first fully automated method, BoneXpert (Visiana, Hørsholm, Denmark), was developed.[107] The BoneXpert software can calculate TW2, TW3, and GP scores with a precision within 0.18 years compared to a manual precision of 0.58 years for the same radiographs.[108] With original data from 1559 images, BoneXpert results had an SD of 0.42 years (95% CI, 0.37 to 0.47 years) compared to the GP method, and an SD of 0.8 years (95% CI, 0.68 to 0.93) compared to the TW3 method.[107] When used with a Japanese cohort, BoneXpert performed excellently (SD, 0.17 years; 95% CI, 0.15 to 0.19 years) compared to manual readings (SD, 0.72 years; 95% CI, 0.68 to 0.76 years).[109] The height prediction model in BoneXpert, when applied retrospectively to 1124 children aged 6 years, performed well; the root-mean-square deviation between predicted and actual heights was 2.8 cm for boys and 3.1 cm for girls.[110]

Hand radiographs have conventionally been used to evaluate bone age, but new work is being done with dual-energy radiograph absorptiometry (DXA), ultrasonography, and MRIs.[111, 112] Although most children never have DXA scans performed, being able to simultaneously determine skeletal age and bone density may be convenient in a select pediatric population. In a small cohort of 38 children, additional DXA readings with Lunar iDXA (GE Healthcare, Little Chalfont, UK) of the left hand showed excellent agreement with an interclass correlation coefficient of 0.97 between traditional films and DXA readings.[111] Children with

a delayed bone age often have an inappropriately low bone mineral density *z* score because they are compared with other children of the same chronologic age.[112] When bone age is assessed with DXA, the bone mineral density *z* score can be recalculated according to bone age rather than chronologic age. Ultrasonographic devices, including BonAge (BeamMed Ltd, Petah Tikva, Israel), are also being used, but their accuracy is questionable.[113,114] Initial data from magnetic resonance scanners show good interrater agreement. Drawbacks to using magnetic resonance scanners include increased cost and the need for patients to remain motionless for 2.5 minutes, which may be too long for young children.[115–118]

CONCLUSIONS

Knowing a child's skeletal maturation may be a time-effective and cost-effective way to direct further diagnostic testing, provide a diagnosis, and even predict a prognosis. Laboratory testing of children often becomes expensive and invasive while providing low clinical yield. Ordering a bone age test may help augment the workup, perhaps narrowing the differential diagnosis, and decrease the required laboratory testing and the need for subspecialty evaluation in certain situations. Furthermore, a bone age test is minimally invasive, which is an important concern for those who care for children.

Despite their popularity and wide application, current methods of assessing skeletal maturation are based primarily on a white population and are not necessarily generalizable to children of other ethnicities, particularly African and certain Asian backgrounds. The limitations are even more important when bone ages are used in high-stake decisions. Further debate is needed on the risks and ethics associated with using bone age for nonmedical purposes. Many newer methods, which may be calibrated to specific populations, may perform better for a wider range of ethnicities, but more data are needed.

ABBREVIATIONS

CI: confidence interval
DXA: dual-energy radiograph absorptiometry
GP: Greulich-Pyle
TW: Tanner-Whitehouse
TW2: Tanner-Whitehouse, second edition
TW3: Tanner-Whitehouse, third edition

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