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Human Body Composition: In Vivo Methods

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Ellis, Kenneth J. Human Body Composition: In Vivo Methods. *Physiol. Rev.* 80: 649–680, 2000.—In vivo methods used to study human body composition continue to be developed, along with more advanced reference models that utilize the information obtained with these technologies. Some methods are well established, with a strong physiological basis for their measurement, whereas others are much more indirect. This review has been structured from the methodological point of view to help the reader understand what can be examined with each technique. The associations between the various in vivo methods (densitometry, dilution, bioelectrical impedance and conductance, whole body counting, neutron activation, X-ray absorptiometry, computer tomography, and magnetic resonance imaging) and the five-level multicompartment model of body composition are described, along with the limitations and advantages of each method. This review also provides an overview of the present status of this field of research in human biology, including examples of reference body composition data for infants, children, adolescents, and adults.

I. HISTORICAL BACKGROUND AND CADAVER STUDIES

Analyses of tissue biopsies have long been a part of the practice of medicine and have contributed greatly to our fundamental knowledge of the basic physiology and metabolism of the human body. The removal of a small amount of tissue from a living subject, be it of bone, muscle, skin, fat, or visceral origin, is technically rather simple, although the procedure is not always comfortable or without risk for the subject. The performance of precise analyses of the makeup of the excised sample is possible with today's advanced technologies. However, it can be very difficult to accurately extrapolate from a single tissue sample to a complete organ, much less to the whole body; extrapolation is often the source of substantial error when estimating total body composition. Notwithstanding this limitation, most of our information about the composition of the human body has been derived in this manner and has been compiled over the years into the concept of the Reference Man (296).

Most of the studies of the human fetus and infants were conducted in the earlier part of the 1900s (105, 130, 157, 223). Direct chemical analyses of the adult whole body are much more limited. In the 1950–1970s, there were the classic works of Widdowson and co-workers (342–344), who examined both infants and adults, whereas Forbes and co-workers (116, 118, 119) reported cadaver analyses of adults only. Whole body human cadaver analyses for ages between infancy and adulthood do not exist, except for the data of one 4.5-yr-old male child, who died of tuberculous meningitis (344). More recently, Knight et al. (164) performed two adult cadaver assays, mainly focused on the determination of total body nitrogen. Complete dissections of adult human bodies also have been performed, with subsequent reports on the variations in organ weights, but not the chemical or molecular makeup of the body (5, 48, 200, 201, 214, 220). These limited data showed that the chemical composition of the body's various tissues is relatively constant among individuals, although it is not constant from birth. These data represent the direct chemical assay of the whole human body and have served as the reference base for the development of various models of human body composition. With the exception of the total body nitrogen measurement, none of the newer in vivo methodologies has been directly verified with human cadaver analysis. In the following sections of this review, the various methods currently available for assessment of body composition are described, pertinent data obtained with each method are summarized, and the relevance of each method to an integrated five-level multicompartment model is discussed. Wherever appropriate, translational relationships among the various levels will be provided for specific body composition compartments. In the final section, reference body composition data or prediction equations for the full life span are provided. This review is intended to present a status report of this field of human biology, to stimulate the interested reader to look further, and to provide the necessary references to assist in that search for knowledge.

II. BODY COMPOSITION MODELS

There is an abundance of anthropometric data on the human body, including measurements of skinfold thickness at numerous sites, circumferences and lengths at various body parts or regions, and a number of weight-for-stature indexes. These anthropometry-based models have been developed to predict body composition for all age groups (29, 183, 186, 258). These anthropometry-based estimates of body composition are not the focus of this review, nor are methods such as ultrasound for the replacement of skinfold calipers (22, 158, 310).

A. Two-Compartment Models

Some of the earliest information about the composition of the human body was based on chemical analyses of specific organs, and occasionally of the whole body. Development and application of the classic two-compartment (2-C) model of body composition have accelerated in recent years because of the association of excess body fat with increased risk for cardiovascular diseases. In the basic 2-C model, the body is divided into two parts. One consists of body fat, and all the remaining tissues are lumped together into the part known as the fat-free mass (FFM). The direct measurement of body fat mass has never been easy and remains a significant challenge for most body composition techniques. However, if one can determine the total FFM, then body fat can be defined indirectly as the difference between body weight and FFM. The 2-C model, which has been used in body composition research for more than 50 years, continues to serve a vital role, especially in the evaluation of newer technologies focusing on body fat assessment.

The earliest and probably the most frequently used 2-C model is based on the measurement of total body density. The most common method is hydrodensitometry or UWW, which can be traced to the pioneering work of Behnke et al. (21). It is interesting that this method primarily evolved at universities with a special focus on body fitness, often relating the measurement to human kinetics, exercise, and sports performance. At the same time, two nuclear-based methods, ^{40}K counting and dilution with radioactive water, each of which required more sophisticated technologies than UWW, were also emerging for use with the 2-C body composition model. For the assessment of body fatness with either of these nuclear-based models,

the water or potassium content of the FFM had to be measured, and their relative concentrations were assumed to be constant for all ages: 0.732 l/kg for body water (234) and 68.1 meq/kg for body potassium (117). Likewise, the density of the FFM for the 2-C model was assumed constant. (21) As long as healthy young white adults were being studied, use of these three constants was satisfactory. However, when the populations included very young or old subjects, different ethnic groups, or subjects with certain diseases, it quickly became evident that these "constants" were, at best, only average values that were often population specific.

B. Three-Compartment Models

To reduce the limitations encountered with the 2-C models, it was only logical to expand to a three-component (3-C) configuration. This approach required that the UWW measurement include a measure of total body water, usually by the isotopic dilution method. In this 3-C model, the FFM is divided into two parts: its water content and the remaining solids (predominately protein and minerals). For this 3-C model, the density of water, fat, and body solids are used. The results obtained using this model provided some improvement over the basic 2-C model for healthy adults and older children. However, for patients with significantly depleted body protein mass and/or bone mineral mass, the estimated values for the density for the solids compartment would be incorrect; thus the final estimate of body fat mass was also inaccurate.

C. Four-Compartment Models

To extend the basic 2-C UWW model to four compartments, one would need an accurate measure of the protein and mineral compartments, in addition to that of total body water. For this four-component (4-C) UWW model, the densities for body protein and bone mineral can be assumed as 1.34 and 3.075 kg/l, respectively (296). However, to obtain a measure of the mass of each of these body compartments, two additional measurements [neutron activation analysis for body protein and dual-energy X-ray absorptiometry (DXA) for bone mineral content] would be needed. This requirement, therefore, introduces somewhat of a dilemma with the use of the 4-C UWW model because if these two additional techniques are used, then they can be used directly to provide an accurate estimate for the body fat mass without the need for the UWW measurement. For the 4-C UWW model, the DXA value for the bone mineral compartment is relatively commonly available, whereas only eight research centers worldwide have access to the direct measurement of body protein mass. It is more common practice with the 4-C UWW model that the protein mass is assumed proportional to the bone mineral mass, independent of age and gender. If one is interested in monitoring short-term changes in fat mass, approximation of the mineral mass is acceptable because this component of the 4-C model will not change significantly for the individual even over relatively long time periods. Changes in the mass of the protein component, however, may be more of a concern if not accounted for accurately. Furthermore, it is rare that significant changes in fat mass will not be accompanied by changes in the size of the body cell mass or protein mass (56, 58, 329).

An alternate 4-C model, which does not require the UWW measurement, has also been developed. In this model, the body's FFM is divided into three basic cellular or physiological compartments: body cell mass (BCM), extracellular water fluid or water (ECW), and extracellular solids (ECS). As defined by Moore et al. (221), BCM can be based on the measurement of whole body potassium (obtained by ^{40}K counting, described in sect. VI*A*) or dilution with a radioactive ^{42}K tracer in plasma. In the determination of the ECW compartment, the dilution methods (described in sect. IV) using bromide or sulfate compounds as the tracer have been developed (76, 77, 126). The ECS compartment can be defined on the basis of total body calcium or bone mineral content (55, 58, 296). Fat-free mass is then defined as BMC + ECW + ECS, and total body fat mass as body weight minus FFM. One of the limitations with this 3-C model for FFM is that the measurement errors are cumulative and transfer directly in mass units to the final estimate for body fat mass.

D. Multicompartment Models

It should be relatively clear to the reader at this point that with each additional measurement it may be possible to extend the number of compartments in the body composition model. Each additional measurement, however, must be compositionally independent of the previous measurements. For example, a measurement of total body chloride (TBCl) can be used instead of the bromide (Br) dilution method for the estimation of ECW volume (75, 286, 350). However, if both TBCl and Br dilution are performed at the same time, no additional information about ECW is obtained. On the other hand, if these two measurements are performed, they can provide separate confirmations for ECW volume that may not be obtained with a single measurement technique; that is, if both TBCl and Br dilution predict an abnormal state, for example, then the probability of a true abnormal condition is extremely high. If only one method is used, then there are technical or model limitations resulting in increased uncertainties associated with that method. Whenever possible, it is best to use repetitive or overlapping methods if

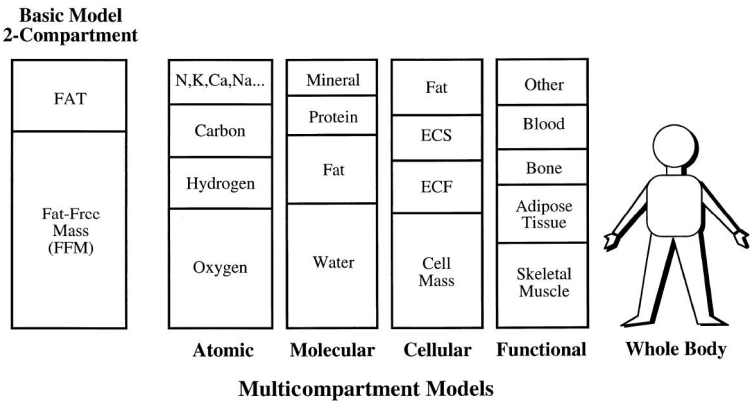

FIG. 1. Basic two-compartment model and five-level multicompartment model of body composition. ECS, extracellular solids; ECF, extracellular fluid. [Modified from Wang and co-workers (332–335).]

confirmation of a normal or abnormal status is the targeted outcome.

Another example is the simultaneous measurement of body carbon and body hydrogen (by neutron activation) as assays for body fat mass and total body water, respectively (161, 178, 286). This information is a duplication of that obtained using DXA for fat mass and deuterium dilution for total body water. Alternately, the measurements of body nitrogen and body potassium can be used together to derive estimates of the skeletal muscle mass, nonmuscle lean mass, and visceral mass (33, 34, 55, 247). Techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) also provide useful information about anatomical structure and can be used to monitor specific organs. Multiple slices are needed to reconstruct volumes, from which mass can be estimated if density is known. These two latter scanning techniques should not be viewed as equivalent to the basic chemical composition model, because in many diseases the apparent volume can be normal, when the chemical composition is significantly abnormal.

A survey of the literature for the last 50 years will show there was an evolutionary process from the basic 2-C models to the presently popular 4-C models of body composition. Wang et al. (335), however, had the insight to collate all of this information and to present it as a comprehensive, five-level model of body composition. This five-level model, illustrated in Figure 1, has become the standard for body composition research. The five levels of the model are as follows: elemental, molecular, cellular, tissue systems, and total body. It is interesting to note that the basic 2-C models tend to start at each end of the spectrum (for example, ^{40}K counting is an elemental model, while body density is an example of a whole body model). As each model includes more measurements, it tends to migrate toward the cellular or physiological model. At each level (examples are presented in Table 1), equations can be used to describe that level within the total model. In addition, there are translational equations between levels, as well as hybrid or mixed level models. In general, the relationships between chemical or elemental composition (amounts of oxygen, carbon, hydrogen, nitrogen, calcium) and the molecular structure of tissues (water, protein, lipids, bone mineral) remain relatively

TABLE 1. *Selected equations related to the five-level multicompartment model*

Elemental level

Body Wt = TBO + TBC + TBH + TBN + TBCa + TBP + TBK + TBCl + TBNa + TBMg + . . .

Molecular level

Body Wt = lipid mass (fat) + total body water + total body protein (TBPr) + bone mineral (OM) + soft tissue mineral (STM)

Cellular level

Body Wt = body cell mass (BCM) + extracellular water (ECW) + extracellular solids + fat

Tissue system level

Body Wt = adipose tissue (fat + cells) + skeletal muscle (SM) + bone (mineral + fluid + marrow) + other tissues

Translational equations between cellular, molecular, and elemental levels

TBCa = 0.340 BMC
TBN = 0.161 TBPr
TBC = 0.759 TBLipid + 0.532 TBPr + 0.018 BMC
TBK = 120 BCM
TBCl = 111 ECW
TBLipid = 1.318 TBC − 4.353 TBN − 0.070 TBCa
TBPr = 6.21 TBN
OM = 2.941 TBCa
STM = 2.75 TBK + TBNa + 1.43 TBCl − 0.038 TBCa

TB, total body for the elements; O, oxygen; C, carbon; H, hydrogen; N, nitrogen; Ca, calcium; P, phosphorus; K, potassium; Cl, chlorine; Na, sodium; Mg, magnesium; BMC, bone mineral content. For more detailed discussion of these and other equations for the 5-level multicompartment model of body composition, see References 332–335.

fixed in both health and disease. Consequently, the reconstruction of body composition from the elemental level is often more reliable and minimizes the assumptions related to tissue density, hydration, and/or structure. In many ways, an accurate in vivo chemical profile of the human body can serve as a replacement for the classical wet chemistry assays used previously to study human cadavers.

III. BODY DENSITY AND VOLUME MEASUREMENTS

A. Underwater Weighing

Because of its early development and widespread use, the measurement of body density (D_b) is often referred to as a gold standard for body composition measurements, even though it is only a 2-C model. The most commonly used method for determining body density is UWW, which requires the subject to be completely submerged in water (21). The volume of water displaced and/or the subject's weight underwater, combined with the subject's laboratory weight, are used to calculate the density (D_b) of the whole body. There is little problem obtaining an accurate measure of body weight (186); the limitations and restrictions are associated with the estimates of body volume and the residual lung volume (36, 160, 291, 346).

In the classic 2-C model of body composition, body weight can be divided into its fat (f_{fat}) and fat-free fractions (f_{FFM}), such that $1/D_b = f_{fat}/D_{fat} + f_{FFM}/D_{FFM}$, where D_{fat} and D_{FFM} are the densities for the fat and FFM compartments, respectively. The assumption that the density of fat is relatively constant is reasonable (107, 200, 312). However, the heterogeneous nature of the FFM compartment (see sect. II) quickly leads one to question the validity of a constant density for this compartment. There may be individual variations related to gender and ethnicity (62, 279), as well as individual changes in density that occur with growth, sexual maturation, aging, physical activity, and a number of diseases (72, 150). Thus 3-C and 4-C models for UWW were developed that require additional measurements of the primary components of the FFM, namely, water, protein, and mineral (121, 184). The types of equations currently used to estimate body fatness, along with the body composition technique required for each of these models, are presented in Table 2.

The UWW methods were developed mainly as a means to measure body volume to assess body fatness, expressed as a percentage of body weight (%fat). Even if the body weight and volume could be measured without error, there would still be considerable uncertainty regarding the individual's %fat estimate due to normal variations in body hydration, protein, and mineral content. It has been estimated that the total cumulative error for body fatness (%fat) is on the order of 3–4% of body weight for the individual (11, 150, 290). Hence, it has been recommended that without adequate corrections for variations in the water and mineral fractions of FFM, densitometry should not be used as a criterion or reference method for heterogeneous populations (212). If one is required to make these additional measurements to correct the basic 2-C UWW estimate, it becomes controversial whether or not the UWW measurement itself is even needed. However, in cases such as pregnancy, where even minimal radiation exposure of the fetus is to be avoided, UWW should be considered.

TABLE 2. *Equations for 2-C, 3-C, and 4-C UWW models used to estimate %fat*

Model	Equations for %Fat	Additional Methods	Reference No.
2C	$100 \times (4.95/D_b - 4.50) \times 100$		290
	$100 \times (4.570/D_b - 4.142)$		30
3C	$100 \times (2.118/D_b - 0.78f_{TBW} - 1.354)$	D_2O	291
	$100 \times (6.386/D_b - 3.96f_{MIN} - 1.354)$	DXA or NAA	184
4C	$100 \times (2.747/D_b - 0.714f_{TBW} + 1.146f_{bone} - 2.0503)$	D_2O and DXA	284

D_b, body density [obtained by underwater weighing (UWW) technique]; f_{TBW}, total body water/body weight (requires isotope dilution measurement); f_{MIN}, total mineral/body weight (requires X-ray absorption or neutron activation measurement); f_{bone}, bone mineral/body weight (requires bone mineral measurement). Additional methods refer to methods needed in addition to UWW: DXA, dual-energy X-ray absorptiometry; NAA, neutron activation analysis; D_2O, deuterium dilution.

Unfortunately, some of the technical adjustments, such as the residual lung volume correction required for all the UWW models or the body water and bone mineral measurements for the 3-C and 4-C models, are not routinely performed but are instead approximated using prediction equations. Hence, it is important to understand the limitations in accuracy imposed under these conditions on the %fat estimate. For the residual lung volume correction, the most commonly used method is oxygen dilution with a closed-circuit spirometer system. For older subjects or those with impaired pulmonary function, an open-circuit nitrogen washout procedure may be better (346). In either case, it has been shown that this correction introduces the major source of error for the %fat value. For example, an error of 100 ml for the residual lung volume translates to an uncertainty of ~1%. If residual volume is not measured, but instead estimated from equations, then the prediction error easily increases to 300–400 ml in a given subject, which produces an added 3–4% uncertainty in the %fat value. The effects of various types of measurement errors on the %fat value are given in Table 3. For example, an equivalent percentage error in residual volume or underwater weight will produce the

TABLE 3. *Effect of errors in residual volume, underwater weight, body weight, and water temperature when the true %fat is 15% for an individual*

Error in	If Underestimated by		True Values	If Overestimated by	
ΔResidual volume, ml	−400	−100	1.2 L	+100	+400
	(%BF 17.8	15.7	15.0	14.3	12.2)
ΔUnderwater weight, g	−50	−20	3.36 kg	+20	+50
	(%BF 15.4	15.1	15.0	14.9	14.6)
ΔBody weight, kg	−0.5	−0.1	70.0 kg	+0.1	+0.5
	(%BF 15.3	15.1	15.0	15.1	15.3)
ΔWater temperature, °C	−1.0	−0.5	36.0°C	+0.5	+1.0
	(%BF 15.2	15.1	15.0	15.1	15.2)

Δ, Change; %BF, percent body fat.

same effect for the %fat value, whereas an error of similar magnitude for body weight will result in a much lower uncertainty. A 1°C change in the water temperature, however, introduces only a small effect on the final %fat value.

B. Air-Displacement Plethysmography

In recent years, the UWW technique has begun to be replaced by air-displacement plethysmography, where the subject is immersed not in water but in a closed air-filled chamber (67, 207). The system consists of two chambers: one for the subject and the other serving as a reference volume (see Fig. 2). With the subject in one chamber, the door is closed and sealed, the pressure increased slightly, and a diaphragm, separating the two chambers, is oscillated to slightly alter the volumes. The classic relationship of pressure versus volume, at a fixed temperature, is used to solve for the volume of the subject chamber. A clear advantage of this technique compared with the UWW measurement is that the subject does not have to be submerged in water; however, all of the technical limitations related to the true volume that were noted for the UWW method remain. Multiple readings over a short period of time can be obtained, which will help to average out some of these concerns. Preliminary studies in healthy adults have shown very good agreement between the plethysmographic and UWW methods (67, 207, 208, 274). However, the accuracy of the plethysmography measurement in children has not been fully tested. These instruments presently are designed for adults and will require significant modifications and improvements if the technique is to become useful for monitoring smaller subjects, including infants.

Even if all the technical limitations can be solved or corrected, we are still left with the question of the physiological accuracy of using a common FFM density among individuals (a problem common to all 2-C models). The results of anatomical studies (48), as well as studies based on chemical models (150, 185, 345), appear to indicate that the densitometric assessment for many individuals has poor accuracy; that is, the normal variation in true FFM densities within a population, compared with an average or fixed value for the same population, will ultimately determine the accuracy for that individual. The

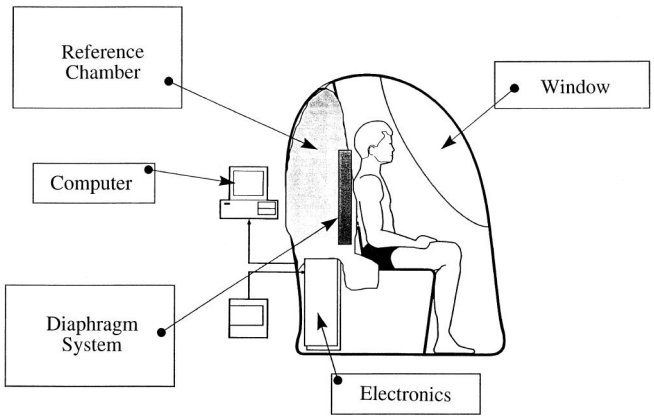

FIG. 2. Drawing of the general configuration of an air-displacement plethysmography system. [Modified from Dempster and Aitkens (67).]

assumption of a fixed density will produce a larger error of FFM than the cumulative technical errors associated with the density measure itself. Furthermore, it is well known that the composition of the FFM changes with growth and maturation (81, 83, 95, 111–113, 140–142, 352) and during aging (55, 78, 114), as well as in many diseases (52). Hence, without additional knowledge of the composition of the FFM, the 2-C volume displacement technique may best serve to identify outliers in a population or the detection of changes in fatness in the individual over short periods of time.

IV. DILUTION METHODS

A. Basic Principle

The basic principle of the dilution techniques for body composition analysis is that the volume of a compartment can be defined as the ratio of the dose of a tracer, administered orally or intravenously, to its concentration in that body compartment within a short time after the dose is administered. Typically, two fluid samples (blood, saliva, or urine) are collected: one just before administration of the dose, to determine the natural background levels, and the second sample after waiting a sufficient amount of time for penetration of the tracer within the compartment of interest. If it is possible that a significant amount of the tracer might be excreted before equilibration is reached, then a cumulative urine sample must be collected to adjust the dose estimate. Alternately, multiple blood samples can be collected, and the tracer content extrapolated to time zero (77, 276). Inherent in any tracer dilution technique are four basic assumptions: *1*) the tracer is distributed only in the exchangeable pool, *2*) it is equally distributed within this pool, *3*) it is not metabolized during the equilibration time, and *4*) tracer equilibration is achieved relatively rapidly. If any of these requirements is violated, then the ratio of administered dose to fluid concentration must be adjusted. For the measurements of total body water (TBW), ECW, and intracellular water (ICW), corrections for overexpansion, nonequilibrium, and excretion of the tracers are needed (13, 126, 275). In mathematical terms, the equation that describes the dilution principle is

$$V = k_1 \cdot k_2 \cdot k_3 \cdot k_4 \cdot \{(D - E)/([d_t] - [d_0])\}$$

where the k values are constants used to correct for differences with each of the basic model, D is the tracer dose, E is the amount excreted during the equilibration period, $[d_t]$ is the tracer concentration in the fluid sampled after *time t* following the administration of the dose, and $[d_0]$ is the baseline concentration before the tracer.

B. Total Body Water

For the molecular (level 2 model) and higher levels of the multilevel model, the single molecule that constitutes the highest fraction of body mass is water. In healthy adults, TBW constitutes ~73% of the FFM or 60% of body weight for nonobese subjects (171). These fractional contents, however, are not constant across the life span (112), nor are they invariant with diseases (171, 276). At full-term birth, a healthy infant's TBW/FFM is typically 80–83% of FFM, which then decreases rapidly over the next 3–5 yr until the hydration fraction reaches that observed for adults. The change in hydration reflects a change in the ratio of water between the intracellular and extracellular compartments (112). In some clinical conditions and with certain drugs, the body can retain or lose significant amounts of water. In the healthy state, TBW tends to be well regulated, although a loss of only 15%, such as in dehydration, can be significantly life-threatening. Wang and co-workers (171) have recently reexamined the classic concept of a fixed "hydration constant" and have shown that even with significant changes in the extracellular-to-intracellular ratio, the hydration ratio (TBW/FFM) remains relatively firm. This aspect of body composition is important if one is interested in monitoring body fat mass where fat is defined as body weight minus FFM and the measurement technique is based on parameters of body water. However, if the interest is in the body cell mass (i.e., intracellular water compartment) or extracellular water space (such as in dehydration or edema), then measurement techniques that respond only to total body water are less useful, if at all.

The earliest, and still the most direct, in vivo measurement technique for TBW is that based on the dilution principle, using a tracer dose of labeled water (tritium, deuterium, or oxygen-18) and collection of two body fluid samples (blood, urine, or salvia), one predose and the second after an equilibration time of ~2–3 h. The method of analysis is dependent on the choice of tracer: radioactive β-counting for tritium, mass spectroscopy for ^{18}O, and infrared absorption, gas chromatography, or mass spectroscopy for deuterium. Each of these methods has received periodic reviews (275–277, 285, 311, 347). It has been shown that 2–4% of the hydrogen tracers exchange with nonaqueous hydrogen, but only ~1% of the ^{18}O tracer (275, 276). For each of these tracers, the estimated error for a TBW measurement is typically <1 kg. For Reference Man (296), this uncertainty in TBW translates to an error of 10% (~1.4 kg) for the absolute fat mass, which translates to 2% for the %fat estimate. In general, TBW values obtained using the dilution technique are considered the reference or criterion values for comparison with alternate measurement techniques (see sect. v).

C. Extracellular Water

The dilution techniques can be used to identify the body's exchangeable electrolyte pools, which are not necessarily the same as the total body content (139, 256, 311). The physiological importance of the exchangeable pools, however, especially at the cellular level (level 3 of multilevel model) makes them suitable for monitoring the body's extracellular and intracellular fluid compartments (28, 43, 139). To measure the volume of ECW, the basic dilution techniques are the same as those used to measure total body water, except the tracer is added to the water, and the body fluid most often sampled is plasma (28, 75, 348). The tracer most commonly used is nonradioactive Br administered orally, with a second plasma sample usually collected ~3–4 h later, although complete equilibration may not have been reached (327). The analytical Br assay in most common use is high-pressure liquid chromotography (211, 276), although a few investigators have used X-ray fluorescence, spectrophotometric, or mass spectrometry techniques (159, 255, 319).

D. Intracellular Water

Measurement of the ICW volume can be obtained using dilution of a radioactive potassium (^{42}K) tracer. This isotope, however, is short lived ($t_{1/2} = 12.4$ h) and is no longer routinely commercially available; hence, measurement of the exchangeable potassium pool is rarely performed. The development of the direct in vivo measurement of total body potassium (TBK) by whole body counting (79) contributed to the decline of the ^{42}K dilution method. The most common practice in use today to estimate ICW is to orally administer a combined D_2O plus Br dose, from which TBW and ECW are determined. Then, ICW is defined as their difference (ICW = TBW − ECW). Unfortunately, the measurement errors (±1 liter error for TBW and ±1.5 liter error for ECW) are cumulative, such that the uncertainty for the ICW estimate is typically ±2–3 liters. Hence, this approach should be considered adequate only for determining the mean ICW value for a population and not necessarily that of an individual. The direct measurement of TBK can normally be obtained with a considerably lower error (see sect. vi) and provides a reliable marker for ICW (42, 91, 221, 249).

V. BIOELECTRICAL IMPEDANCE AND CONDUCTANCE METHODS

A. Bioelectrical Impedance Analysis

The ability of tissues, and therefore the whole body, to conduct an electric current has been recognized for more than a hundred years. The aqueous tissues of the body, due to their dissolved electrolytes, are the major conductors of an electrical current, whereas body fat and bone have relatively poor conductance properties (229, 313). Although significant technical problems eliminated the viability of many electrical methods for in vivo body composition analyses, the basic principle of measuring TBW had been suggested a number of years ago (153, 230). In the 1980s, when several commercial instruments designed for bioelectrical impedance analysis (BIA) were marketed, there was a resurgence of interest in this approach for human body composition analysis. At present, it is probably the most frequently used method, due mainly to the relatively inexpensive cost of the basic instrument, its ease of operation, and its portability.

The BIA measurements are performed using four electrodes: usually two are attached at the wrist and two at the ankle. For the single-frequency measurement (typically at 50 kHz), a weak alternating current is passed through the outer pair of electrodes, while the voltage drop across the body is measured using the inner pair of electrodes from which the body's impedance is derived. To convert this information to a volume estimate, two basic assumptions are used. First, the body can be modeled as a isotropic cylindrical conductor with its length proportional to the subject's height (Ht). Second, the reactance (X) term contributing to the body's impedance (Z) is small, such that the resistance component (R) can be considered equivalent to body impedance. When these two assumptions are combined, it can be shown that the conducting volume is proportional to the term Ht^2/R, called the impedance index. It should be noted, however, that the human body is not a cylindrical conductor, nor are its tissues electrically isotropic, and the reactance component of the body's impedance is nonzero (225).

At 50 kHz, the body's impedance has both resistive and reactive components. The reactive component is assumed to be related to the portion of the current that passes through cells which act like capacitors that shift the voltage and current out of phase. In electrical terms, the phase angle (ϕ) is defined by the relationship: $\tan(\phi) = X/R$, where $Z^2 = R^2 + X^2$. In healthy adults, the phase angle at 50 kHz is usually in the range of 8–15° (15, 45) but varies widely at high frequencies (46). Several investigators have used the phase angle to assess body composition in various clinical conditions (241–244). In renal patients, for example, the phase angle at 50 kHz is typically <5° and has been interpreted as an indication of an expanded ECW space concurrent with a reduced ICW volume.

A number of electrical-circuit models have been used to describe the general properties of biological tissues (3, 323). One model, shown in Figure 3*A*, has the extracellular resistance (R_e) in parallel with the intracellular resistance (R_i), while the capacitance of cells (C_m) is in series

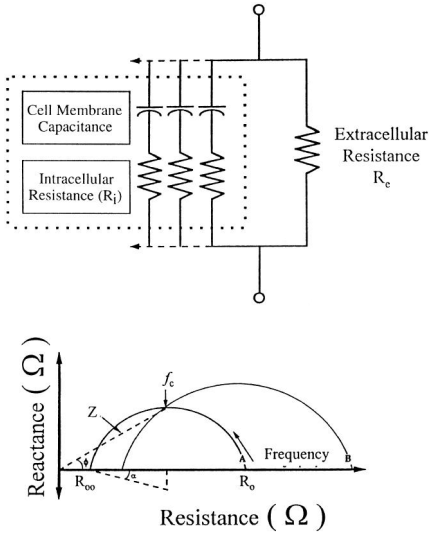

FIG. 3. *A*: electrical circuit used to describe resistance and capacitance of the whole body. *B*: plot of reactance versus resistance as a function of frequency. Curves in *B* illustrate the effects of a change in extracellular volume or electrolyte concentration. *Z*, impedance; f_c, characteristic frequency; R_0, resistance at zero frequency; R_∞, resistance at infinite frequency.

with the intracellular resistance. For this model, the impedance varies as a function of frequency, as shown in Figure 3*B*. At zero frequency ($f = 0$), the current does not penetrate the cell membranes; thus impedance is purely resistive and is equal to that of the extracellular compartment ($Z_0 = R_e$). At infinite frequencies ($f = \infty$), the cells become transparent to the current, such that the impedance is equal to the resistance for a parallel circuit ($Z_\infty = R_e R_i/(R_e + R_i)$). Because measurements are not technically possible at zero or infinite frequency, the Z_0 and Z_∞ values have to be derived mathematically by fitting the shape of the reactance versus resistance curve (60, 203). In the simplest model, Z_0 and Z_∞ are assumed to be the resistance values for the extracellular and total body water space, respectively; that is, for an individual, TBW $\propto 1/R_\infty$ and ECW $\propto 1/R_0$. To calibrate the proportionality constants for these relationships, the TBW and ECW derived by deuterium and Br dilution assays, respectively, are used as the criterion or reference values, and height is used as a measure of the conductor's length.

B. Bioelectrical Impedance Spectroscopy

A more complex model has evolved, based on modification of a mixture theory model (135) and partitioning the whole body into a series of cylinders, each representing various body segments (203, 326). For this model, resistance and reactance measurements are made over a wide range of frequencies. One instrument based on this model is commercially available (Xitron, San Diego, CA), and the technique is often called bioelectrical impedance spectroscopy (BIS). The equations reported for the estimations of extracellular water (V_{ECF}) and intracellular water (V_{ICF}) volumes are

$$V_{ECF} = k_{ECF}/(Ht^2 \cdot Wt^{0.5}/R_e)^{2/3}$$

and

$$(1 + V_{ICF}/V_{ECF})^{5/2} = [(R_e + R_i)/R_i] \cdot [1 + k_\rho \cdot V_{ICF}/V_{ECF}]$$

where Ht is height, Wt is weight, and the R values are the resistance values for the intra- and extracellular compartments. The k_{ECF} and k_ρ values are assumed constant and can be defined in terms of resistivity for the extracellular and intracellular tissues, body density, and body volume (65).

In the impedance locus plot shown in Figure 3*B*, the frequency at which reactance (X) reaches a maximum is called the characteristic frequency (f_C). For the single-frequency BIA method, the 50 kHz that is used is basically assumed to be f_C. In fact, f_C can vary over a wide range of values for healthy individuals (60, 203, 204). It should be pointed out that the shape of the impedance locus shown in Figure 3*B* is not uniquely associated with the electrical-circuit model given Figure 3*A* as other circuits can also produce the same reactance versus resistance response (74, 120, 128, 189). These alternate electrical circuit models, however, tend to be more complicated, and the individual components do not lend themselves to a simple biological interpretation. Nevertheless, this should be kept in mind when translating the results for the simple circuit model into body composition compartments with physiological or clinical significance.

Regardless of the choice of single or multifrequency method, the resistance values obtained are considered as indirect body parameters and therefore must be calibrated with a more direct method of body composition, such as total body water, body potassium, hydrodensitometry, or DXA. Unfortunately, there are almost as many different single-frequency BIA calibration equations in the literature as there are studies, which may indicate that many of these equations are population specific, especially those that include anthropometric predictors (14, 154, 301). A secondary problem has been the use of the basic 2-C hydrodensitometry model as the reference technique without inclusion of the differences reflected by variations in the bone mineral compartment. These uncertainties with

the single-frequency BIA methodology, for example, were major criticisms pointed out at the National Institutes of Health (NIH) technology conference (225); that is, these equations tend to be applicable only for classifying a population, not necessarily individuals within that population. Furthermore, many investigators found that the basic model failed; that is, the impedance index (Ht^2/R) alone was not an accurate predictor and that additional anthropometric terms (i.e., weight, age, gender, race, shoulder width, girth, waist-to-hip ratio, body mass index) were included in the prediction model to reduce the standard error of the estimate. No physiological justification for the added terms was provided. Not withstanding these limitations, several of the most frequently used equations for single-frequency BIA are given in Table 4. The BIA equations have been developed for newborn infants and toddlers, children and adolescents, and all ages for adults. Baumgartner (14), for example, has compiled a detailed list. Although similar types of adjustments have been proposed for multifrequency measurements, the BIS equations do not lend themselves to easy modification. However, for calibration of the BIS measurements, a range of tissue resistivity values has been reported for different populations (96, 98, 103, 295).

C. Total Body Electrical Conductivity

An alternate bioelectrical method used to measure body composition is total body electrical conductivity (TOBEC) (14, 49, 50, 108). This technique is based on the following premise. When the body is placed inside a solenoid or coil that is used to generate a time-varying electromagnetic field, eddy currents are induced in the conductive tissues in the body. These currents are opposed to the direction of flow in the external coil, which causes a perturbation of the external field, resulting in absorption of a small amount of energy (E) in the body, which is dissipated as heat. The amplitude of this effect is governed by the magnitude of the external electromagnetic field, the uniformity of the magnetic field within the coil, the conductivity of tissues, and the cross-sectional area of the body (125). If the body can be approximated by a cylinder of volume V and length L, then $V \propto (E \times L)^{1/2}$, where E is called the "TOBEC number." The conduction volume is assumed to be the body's total

TABLE 4. *Examples of BIA equations derived for the prediction of TBW, ECW, and FFM*

Age Range	Number and Sex	Prediction Equation	SEE	Reference No.
		Single-frequency (50 kHz) BIA equations for TBW		
4–7 days	17	$235.8\ (Wt \cdot Ht^2/R) + 567$	0.76 l	205
<3 yr	65	$0.67\ (Ht^2/Z) + 0.48$	0.36 l	109
5–18 yr	14F, 12M	$0.60\ (Ht^2/R) - 0.50$	1.69 l	63
35–65 yr	67F, 72M	$0.24\ (Ht^2/R) + 0.172Wt + 0.165Ht + 0.039\ (Ht \cdot Wt) - 17.577$	3.47 l	146
19–65 yr	20F, 20M	$0.556\ (Ht^2/R) + 0.096Wt + 1.73$	1.75 l	175
19–42 yr	37M	$0.63\ (Ht^2/R) + 2.03$	2.03 l	192
20–73 yr	28F, 25M	$0.372\ (Ht^2/R) + 3.05\ (sex) + 0.142Wt - 0.069age$	1.61 l	190
19–61 yr	20F, 88M	$0.484\ (Ht^2/R) + 0.1444Wt + 1.356S + 0.105Xc - 0.057age$	1.53 l	353
		Single-frequency (50 kHz) BIA equations for FFM		
10–14 yr	41F, 53M	$0.83\ (Ht^2/R) + 4.43$	2.60 kg	155
7–15 yr	166	$0.406\ (Ht^2/R) + 0.36Wt + 5.58Ht + 0.56\ (sex) - 6.48$	1.68 kg	71
7–25 yr	140M	$0.156\ (Ht^2/R) + 0.646Wt + 0.475AC - 0.116LC - 0.375MX - 2.932$	2.31 kg	132
7–25 yr	110F	$0.182\ (Ht^2/R) + 0.682Wt - 0.185LC - 0.244T - 0.202SS + 4.338$	2.23 kg	132
17–59 yr	41F, 34M	$0.363\ (Ht^2/R) + 0.214Ht + 0.133Wt$	3.06 kg	281
17–62 yr	498F, 1069M	$0.0013Ht^2 - 0.044R + 0.305Wt - 0.168age + 22.668$	2.43 kg (F) 3.61 kg (M)	282
18–50 yr	67F, 84M	$0.756\ (Ht^2/R) + 0.11Wt + 0.107Xc$	2.06 kg	191
16–83 yr	661	$0.34\ (Ht^2/R) + 15.34Ht + 0.273Wt + 4.56sex - 0.127age - 12.44$	2.63 kg	71
65–83 yr	37F, 35M	$0.36\ (Ht^2/R) + 0.359Wt + 4.5sex - 0.20TC + 7.0$	2.50 kg	70
65–94 yr	63F, 35M	$0.28\ (Ht^2/R) + 0.27Wt + 4.5sex + 0.31TC - 1.732$	2.47 kg	16
		Dual-frequency BIA equations for TBW and ECW		
19–64 yr	36M	$TBW = 0.455\ (Ht^2/R_{100}) + 0.14Wt + 3.43$ $ECW = 0.284\ (Ht^2/R_5) + 0.112Wt - 6.115$	2.64 kg 1.94 kg	280
19–65 yr	20F, 40M	$TBW = 0.297\ (Ht^2/R_{224}) + 0.147Wt - 3.637sex + 14.017$ $ECW = 0.099\ (Ht^2/R_{224}) + 0.093Wt - 1.396sex - 5.178$	3.58 kg 1.06 kg	325
19–52 yr	27F, 33M	$TBW = 0.483\ (Ht^2/Z_{100}) + 8.4$ $ECW = 0.229\ (Ht^2/Z_1) + 4.5$	2.27 kg 1.14 kg	69

BIA, bioelectrical impedance analysis; TBW, total body water; ECW, extracellular water; FFM, fat-free mass; Ht, height; Wt, weight; R, resistance; Z, impedance; X, reactance; SEE, standard error of estimate.

electrolyte volume; thus the TOBEC instrument has been calibrated with a measurement of TBW. Two commercial instruments were developed (EM-Scan, Springfield, IL), one sized for infants and the other for adults. The length of an infant's body is sufficiently short that a static measurement can be made; that is, if the outer coils are about twice the length of the body, then the infant can be placed at the center of the coils for the measurement. For adults, the whole body is scanned, and information is collected at 64 positions along the length of the body, and the output is analyzed using Fourier analysis (324). A list of TOBEC calibration equations has also been compiled by Baumgartner (14).

The basic TOBEC concept would indicate that it is relatively insensitive to shifts of fluid or electrolyte between the intracellular and extracellular compartments; hence, it has only been used to monitor TBW (49, 50). However, it was suggested that using multifrequency TOBEC coupled with Fourier analysis might provide a measure of each fluid subcompartment (125, 324), although no subsequent studies have demonstrated this application. The TOBEC measurements have been used mainly to monitor changes in body composition in women during pregnancy or lactation (37, 222), in infants (38, 64, 288), and in childhood obesity (80, 163, 254).

VI. WHOLE BODY COUNTING AND NEUTRON ACTIVATION ANALYSIS

A. Total Body Potassium

Whole body counters were initially built for nuclear research and weapons facilities to monitor workers for possible internal contamination as a result of man-made radioactivity. Fortunately, the number of nuclear accidents involving human exposures has been very rare; the one significant exception being the Chernobyl nuclear power incident in 1986. When monitoring workers, it was noted that a constant peak was evident (later attributed to ^{40}K) for all workers independent of their exposure history. However, it was not until an association between ^{40}K and FFM was reported that this method was developed for body composition use (8, 117, 173). The counting of ^{40}K was the first true in vivo chemical assay of the human body. This isotope makes up ~0.012% of natural potassium and emits a high-energy γ (1.46 MeV) at the rate of ~200 dpm/g K (115, 272, 337). More than 50% of these γ will exit the body, which allows for external counting (156). For a 70-kg young adult male, the body content of potassium will produce $\sim 1.5 \times 10^4$ external γ-rays/min. The rate for a preterm infant (<2 kg body wt) is only ~500 g/min. Although this process contributes to our cumulative lifetime exposure, the health consequences of this internal dose remain unknown (179). Some have argued that the dose may not be harmful and that it may contribute to radiation hormesis (39, 187, 188).

To obtain an accurate ^{40}K measurement in humans, there are three design considerations: *1*) γ-ray detectors with good energy resolution and high efficiency, *2*) adequate shielding around the subject and detectors to reduce the terrestrial and cosmic background levels, and *3*) a data acquisition system that can uniquely identify the 1.46 MeV γ of ^{40}K (79, 156). Whole body counter designs range from the basic "shadow-shield" single-detector configuration to multidetector arrays housed in specially designed shielded rooms (91, 156). Counting times can range from a few minutes to an hour, depending on the reduction in background signal, counting efficiency, and size of the subject (156). The whole body counter located at Baylor College of Medicine (90, 91), for example, was designed for potassium measurements ranging from preterm infants to obese adults (see Fig. 4). The subject is in a supine position on a bed between two arrays of NaI detectors that are inside a room constructed of 20-cm-thick steel walls surrounded by 1-m-thick concrete for shielding. The ^{40}K signal is recorded for 15 min, corrected for background, and converted to a total body potassium (TBK) value. The performance characteristics of this counter are listed in Table 5. Mannequins (also called phantoms) of various sizes are used for calibration of whole body counters (23, 138, 287) and for intercomparison among counters (106, 309).

Total body potassium has been used primarily as a marker for body cell mass as defined by Moore et al. (221). It has also been used to estimate FFM, where the TBK/FFM is based on the classical cadaver work of Forbes and co-workers (117, 118). Custom has almost enshrined these two original conversion factors, although many subsequent studies have consistently reported lower mean potassium concentrations for the FFM (see

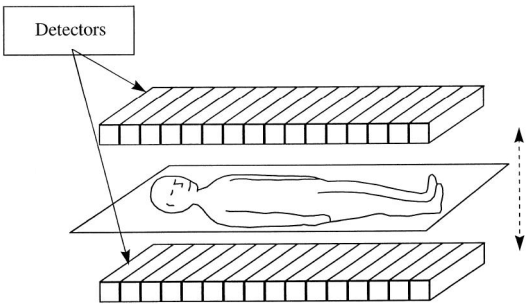

FIG. 4. Example of a multidetector whole body counter designed to monitor body potassium in infants, children, and adults. Distance between detector arrays can be varied to maximize counting efficiency and precision. [Modified from Ellis and Shypailo (90, 91).]

TABLE 5. *Operating characteristics of the whole body counter at Baylor College of Medicine*

	Age Group					
	VLBW	Preterm	Infant	Toddler	Child	Adult
Detectors (*n*)	3	6	12–16	16–20	20–28	30
Age range	30–36 wk	36–44 wk	1–9 mo	1–3 yr	4–12 yr	>13 yr
Weight range, kg	0.5–3.0	1.5–5.5	2.5–10	5–15	15–70	40–130
Height range, cm	25–50	25–60	45–70	60–100	100–180	150–200
cps/g K	0.41	0.50	0.41	0.35	0.33	0.25
Precision, %	3.3	2.0	2.5	2.1	1.7	0.8
Time, min	30	30	15	15	15	15

VLBW, very low birth weight; cps/g K, counting sensitivity (^{40}K counts^{-1} · s^{-1} · K^{-1}). For VLBW and preterm babies, age range refers to gestational age. For more details, see Ellis and co-workers (90, 95).

Table 6). Although the differences for the TBK/FFM are relatively small, this effect is amplified when TBK is used with the 2-C model to derive an estimate for the body's fat mass (248, 334). However, TBK serves as the best choice for normalization of metabolic parameters among subjects (246).

The high precision of the TBK measurement has been established, although its absolute mass accuracy is less firmly established. A direct confirmation of TBK values, for example, has not been obtained by human cadaver analyses, although it has been found to be accurate in animal measurements (unpublished data). Furthermore, when the same tracer dose of ^{42}K was given to subjects representing a wide range of weights and heights, the calibration used for TBK correctly determined the administered dose for these subjects (51). In general, the accuracy of the whole body measurement of TBK is 1–5% for adults, decreasing slightly for the preterm infant (91).

As noted previously, TBK is considered the best body composition index for assessing body cell mass, the body's metabolically active tissues (246). The future research direction of TBK should not focus on its use with the 2-C model to estimated fat, but instead on the more advanced multicompartment models where a measure of BCM is needed. A combination of techniques, such as TBK, BIS, and DXA, should give a fuller assessment in the 3-C model of body composition. This model is the one of interest in diseases, especially those involving abnormal fluid shifts, altered endocrine function, or irregular hormonal profiles.

TABLE 6. *Estimates of the average potassium content of the fat-free mass in adult human beings*

Age Range, yr	Number of Subjects (Female/Male)	TBK/FFM, meq/kg		Reference No.
		Female	Male	
White				
25–50	1/4	64.0*	68.1*	118
21–50†	308/182	57.8	67.8	245
20–79†	62/73	57.9	64.5	55
14–60	104/24	60	65	127
24–56	12/17	62	64.7	177, 293
20–37	17/12	64	66	145
20–90†		66	66	335
24–78†	28/24	56.6	63.9	129, 232
26–93†	10/10	52.0	60.0	151
18–37	/20		63.7	237
Black				
20–79†	28/24	63.1	62.3	129, 232

*Human whole body cadaver analyses were performed. †Total body potassium (TBK)/fat-free mass (FFM) decreases with age.

B. Neutron Activation Analysis

In sections I and II, it was noted that the chemical or elemental model has been the historic reference for body composition analysis. Most of this information has been collected for tissues or organs, and the composition of the whole body has been reconstructed, such as that for Reference Man (296). A substantial paradigm change in the study of whole body composition occurred with the development of in vivo neutron activation analysis (NAA) techniques. These procedures allowed for the direct elemental analysis of the living human body (44, 53, 302). Alternate body composition techniques such as CT, MRI, DXA, electrical impedance (BIA and BIS), and tracer dilution provide information generally related to tissue density or volume, but not chemical content. For this reason, the multicompartment elemental models based on in vivo NAA have become the reference norms most often preferred for evaluation and/or calibration of the alternate techniques (331–335).

A comprehensive list of the procedures, instruments, and applications developed with the in vivo NAA techniques can be found in a series of conference publications (6, 53, 86, 99, 235, 351) and two review papers (44, 302). Combined, these publications provide a detailed historical development of the techniques, a summary of state-of-the-art facilities, and examples of some of the applications in human biology, physiology, and medicine. Today, virtually all the major elements of the body can be as-

sayed in vivo: hydrogen, oxygen, carbon, nitrogen, calcium, phosphorus, sodium, chlorine, and potassium (via ^{40}K counting). In addition, specialized partial-body techniques have been developed for specific elements and/or organs in the body. These elements include cadmium, mercury, iron, iodine, aluminum, boron, lithium, and silicon; the organs are kidney, liver, brain, lung, heart, and thyroid (44, 235, 302).

The basic physics of NAA can be explained simply. When an atom captures a neutron, the atom is transformed to another nuclear state of the same chemical element. This new atom can be stable or radioactive, but it will have excess energy that must be released immediately (typically $<10^{-14}$ s). If the new atom is radioactive, it will decay over time with a known half-life. Thus, when the body is exposed to neutrons, γ-rays are emitted immediately (prompt) and for some time thereafter (delayed), some of which can be detected outside the body using a monitoring instrument like that used for the ^{40}K counting procedure (79, 91).

The number of neutron sources, the type of sources, the physical design of the irradiator, the position of the body within the neutron field, and the detection system will combine to determine the overall precision and accuracy of the analysis (79). Although each of the NAA facilities is similar, no standardization in design exists; however, recent modifications of these systems have been guided by Monte Carlo simulations (73, 298). Phantoms or mannequins that simulate of the range of human sizes and shapes are often used for calibration, and an absolute accuracy of <5% is generally achieved. A recent analysis of the theoretical basis for a prompt-gamma system (298, 299) provides a detailed description of the calibration procedures that are required. Accuracy of NAA is at least as good as that obtained using classical "wet chemistry" techniques and has been shown in animal carcass analyses to be more reliable and precise (90). Although NAA facilities have been in use for more than 30 years, a direct comparison of results between two systems has been reported only recently (194).

The NAA facilities for clinical research have been developed in a number of medical centers (17–20, 90, 195, 269, 299, 328). The two elements most frequently measured are total body calcium (TBCa), using delayed NAA, and total body nitrogen (TBN), using prompt NAA. The reported accuracy and precision are 1–2% for TBCa and 3–4% for TBN. The radiation dose for the TBN measurement is relatively low (<0.3 mSv), whereas that for the TBCa measurement is substantially higher (>3 mSv).

A major disadvantage of the NAA technique is that most of the dose is delivered to the body without the production or detection of a useful signal. To overcome this limitation, pulsed activation schemes are being developed (102, 161, 178, 215, 216, 239, 248). In this case, the detection system is gated on and off to count only at the times of highest probability for an interaction, significantly reducing the overall background signal. Some investigators have found that bismuth germanium oxide detectors offer a significant improvement over the traditional use of NaI detectors for these applications (24, 267). With these modifications, the TBN sensitivity may be improved, possibly 10-fold for the same dose. If NAA is to remain a viable option in the field of body composition research or to be considered for clinical applications, then these newer instruments must be developed further.

Probably the one major concern restraining a more general use of NAA techniques is that of the associated radiation exposure. Therefore, this issue needs to be addressed briefly. First, the environment we live in is not radiation free. The average "natural" background in the United States from all sources (cosmic, terrestrial, radon, ourselves, and man-made) is estimated at 3.6 mSv/yr (47). The doses for each of the in vivo NAA measurements of body carbon, nitrogen, and calcium are ~0.1, 0.3, and 3 mSv, respectively. For comparison, the average dose for a routine chest X-ray for an adult is typically 0.4 mSv, the range being 0.1–1.0 mSv. All clinical or diagnostic radiological procedures involve some risk, and it is essential to weigh the benefits of such measurements against its risks (25). Table 7 provides a list of life experiences with risks comparable to that for the TBN measurement (79). Even though these risks are relatively small, it is essential to continue to explore ways to reduce the doses to the lowest level possible without introducing a significant loss of precision or accuracy.

TABLE 7. *Risk associated with in vivo nitrogen measurement comparable to "every day" risks*

Activity	Type of Death
Modes of travel	
Air (150 mi.)	Accident
Air (Trans-Atlantic flight)	Cancer (cosmic rays)
Car (15 mi.)	Accident
Living conditions/location	
5,000 ft. above sea level (3 mo)	Cancer (cosmic rays)
Living in stone building (2 wk)	Cancer (radon)
Employment conditions	
Working in average United States factory (3 days)	Accident
Working in a United States coal mine (30 min)	Accident
Smoking (1 cigarette)	Cancer

The assumed risk for each activity is that it would result in death (see Refs. 25, 79). Type of death refers to type of event that could cause death. For these calculations, a probability of an occurrence is estimated at ~1 in 5–8 million. By comparison, the average yearly chance (probability) for an individual living in the United States of being killed by lightning is ~1 in 1 million.

VII. DUAL-ENERGY X-RAY ABSORPTIOMETRY

A. Absorptiometric Principle

When an X-ray or photon source is placed on one side of an object, the intensity of the beam on the opposite side of the object is related to its thickness, density, and chemical composition. This attenuation phenomenon is also dependent on the energy of the incident photon and is dominated by two principles at low energies: the photoelectric effect and Compton scattering (251, 257, 341). The attenuation response is nonlinear, such that for a homogeneous material, it can be described by the exponential equation $I = I_o e^{-\mu T}$, where I is the transmitted intensity, I_o is the incident intensity, T is the absorber thickness, and μ is the linear attenuation coefficient. If the thickness of the absorber is known, this relationship can also be expressed as $M = (1/\mu_m) \ln(I_o/I)$, where M is the mass of the absorber and μ_m is the mass attenuation coefficient ($=\mu/\rho$ with ρ as the density of the absorber). If the absorber is composed of two or more materials, then the composite μ_m is the weight sum of the individual mass attenuation coefficients, each weighted for its fractional contribution to the total mass.

The attenuation through bone, lean tissue, and fat is different, reflecting their differences in densities and chemical composition (251). With increasing photon energy, the differences in the attenuation properties for these tissues decrease. On the basis of theoretical and experimental studies (162, 206, 227), it has been shown that if the low-energy (L) photon is ~40 keV, while the high-energy (H) photon is in the range of 70–100 keV, the mass of bone (B) and soft tissue (ST) along the beam path can be expressed as follows

$$M_{ST} = (\mu_{BL} LR_H - \mu_{BH} LR_L)/(\mu_{BH}\mu_{STL} - \mu_{STH}\mu_{BL})$$

$$M_B = (\mu_{STL} LR_H - \mu_{STH} LR_L)/(\mu_{STH}\mu_{BL} - \mu_{BH}\mu_{BL})$$

where LR_H is $\ln(I/I_o)$ at the higher energy and LR_L is the same ratio at the lower energy. Thus, if the relative intensity of the transmitted beam can be measured, and the mass attenuation coefficients are accurately known, estimates of the bone mass and overlaying soft tissue mass can be calculated. This 2-C model is also used when the beam passes through body regions without bone. In this case, the appropriate attenuation coefficients are those for fat (F) and lean (S) tissues, respectively.

It should be evident that DXA is really composed of two separate sets of equations, each used to describe a 2-C model. Dual-energy X-ray absorptiometry does not provide three independent measurements, even though three body composition values [bone mineral content (BMC), lean tissue mass (LTM), and fat mass (FM)] are reported. To accomplish this feat, the manufacturers must assume that the composition of the soft tissue layer overlaying bone has the same fat-to-lean ratio as that for nonbone pixels in the same scan region (162, 206, 227, 251). Typical body images are shown in Figure 5 for the whole body, lumbar region of the spine, and the upper region of the femur. In the case of the whole body scan, ~40–45% of the pixels are classified as containing bone. The remaining pixels are used to estimate the body's fat-to-lean ratio; this value is applied to the soft tissue component in the adjacent bone pixels. Thus the relative lean-to-fat composition of the total soft tissue mass is based on sampling only one-half of the whole body. Some investigators have expressed concerns with this approach as well as those related to a significant change in the hydration of the lean tissues (267). The latter concern, however, has recently been theoretically shown not to significantly alter the estimates for the bone, lean, or fat mass (209, 210, 251, 252).

Total body DXA measurements have not been verified by human cadaver analyses, although several studies have used animal models (31, 32, 94, 213, 240, 253, 303). The DXA-derived values for BMC, LTM, and FM have been compared with a multicompartment model based on elemental NAA and were shown to be in good agreement (148). Additional studies have compared total body BMC with TBCa, showing excellent correlation, but substantial differences in the slope of the regression equations (93, 149, 250). A recent comparison between the two NAA facilities has confirmed their agreement to within 2–3% (194); thus the majority of the differences can be attributed to the DXA technology, presumably reflecting the methods for calibration. When DXA measurements were performed on the same subjects, but with different manufacturers' instruments, there were substantial differences in the individual's body composition estimates (314–316, 318). Some of this effect can be attributed to the way in which the fitting algorithms partitioned the soft tissue mass between its lean and fat components, especially if there was an excessively abnormal fat mass. These effects were also evident when the bone mineral density (BMD) values were calculated, mainly due to a reduction in the number of pixels assigned as containing bone.

B. Bone Mineral Measurements

The primary application of DXA has been to obtain site-specific measurements of areal BMD at the lumbar spine, femur, and forearm (193). The BMD is defined as the ratio of BMC to bone area (BA), where BA is the total area in the planar scan image for all pixels classified as containing bone. It should be noted that areal BMD is not true bone density (in g/cm^3 units), which can be obtained

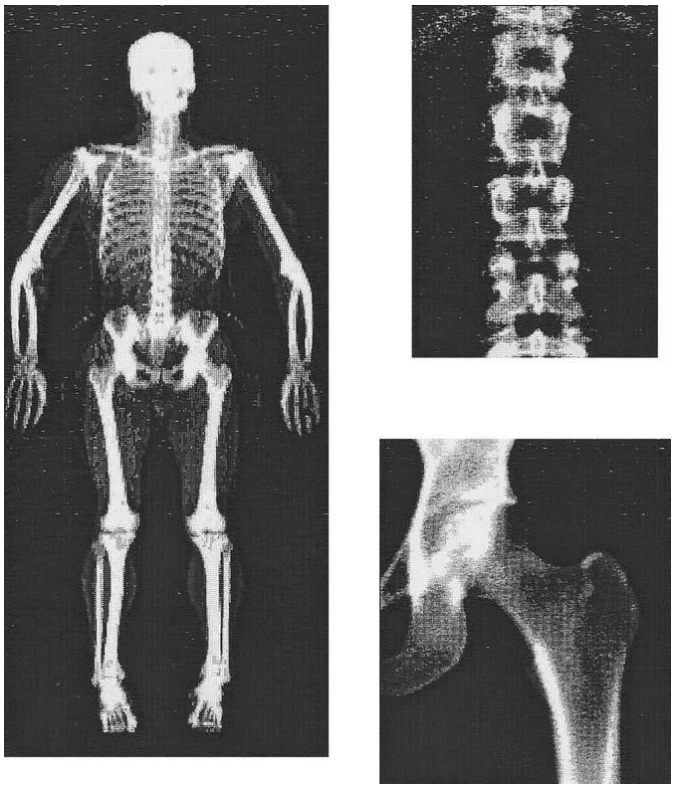

FIG. 5. Total body, spine, and hip scan images obtained using dual-energy X-ray absorptiometry.

via CT. The primary function of calculating BMD is to reduce the biological variance seen in BMC values at all ages, thus increasing the statistical power of detecting abnormal values. A number of alternate schemes have been proposed using the BMC and BA data in various combinations to derive a more accurate estimate of the true bone density (41, 233, 270, 278, 307). None of these, however, has found widespread acceptance for clinical use over the simpler BMD estimate based on the BMC/BA.

The results of a whole body DXA scan provide values for a 3-C model that is somewhat like that of the level 4 multicompartment model in that a specific tissue, namely, skeletal mass, can be examined. Dual-energy X-ray absorptiometry also provides information about the general anatomical distribution of bone within the body. The DXA-derived estimates for FM have been shown to agree well with values obtained using the 2-C models or level 1 and level 2 models (149, 150). It should be noted that although DXA provides a measure of the body's nonbone lean tissue compartment, it does not specifically measure protein mass; that is, the estimate for the lean mass obtained using DXA can vary independently of the true changes in protein mass (87, 88).

Notwithstanding these limitations, the DXA technology represents a significant advancement in measurement techniques for body composition. This procedure, which requires some cooperation by the subject, can be performed within minutes at a very low dose (usually <10 μSv), and the results can be obtained immediately. Dual-energy X-ray absorptiometry has clearly attained a dominant role in the measurement of bone loss for clinical diagnosis of osteopenia and osteoporosis (181). Newer-generation DXA instruments using only fan-beam technology have been developed but need further study to determine their accuracy for monitoring changes in body composition (12, 92, 162).

C. Triple-Energy X-ray Techniques

Several research centers are performing feasibility studies that are focused on the development of triple-

energy X-ray absorptiometry. This would be an extension of the DXA technique, but the energies must be uniquely selected. In theory, if the three energies are from the Compton scattering, photoelectric, and pair production regions, then it may be possible to obtain estimates not only for bone and fat, but also those of body water and protein mass (172, 209, 304–306).

VIII. MAGNETIC RESONANCE IMAGING AND COMPUTED TOMOGRAPHY

A. Magnetic Resonance Imaging

The strength of the earth's magnetic fields is very weak, such that atoms and molecules in the body are in random orientations. However, when the body is placed in a strong magnetic field (orders of magnitude greater than the earth's fields), some nuclei will attempt to align with or against the magnetic field (68). Hydrogen protons (^{1}H), in particular, have a high affinity for alignment with the magnetic field. Other atoms found in the human body (^{13}C, ^{19}F, ^{23}Na, ^{31}P, and ^{39}K) also display these properties, but at a substantially lower response than that for hydrogen atoms. Although only a small percentage of nuclei will be aligned, the number is sufficient to detect a change in their orientation when the magnetic field is removed or altered. The frequency at which nuclei for each element will flip or precess (relative to the direction of the constant magnetic field) is called the Larmor frequency. When radiofrequency (RF) energy, at the Larmor frequency, is applied perpendicular to the direction of the magnetic field, the nuclei will absorb this energy and change alignment. When the RF field is off, the nuclei will lose their alignment and release the stored energy. The intensity of this signal can be used to measure the number of hydrogen nuclei of the tissue. This process can be repeated at each position along the length of body until the whole body is mapped and cross-sectional MRI images at each slice can be generated. Magnetic resonance imaging is successful because hydrogen, found mainly in water, is one of the most abundant nonbound elements in the body. For other elements, their concentrations in the body are lower and the Larmor frequency changes, thus requiring an increased magnetic field strength if imaging is to be considered (302).

If the hydrogen densities of adipose and lean tissues were markedly different, then it would be possible to develop images based solely on their number of nuclei. This is not the case. Thus, to enhance the contrast between lean and fat tissues, a second feature of the nuclei, called relaxation time (*T1*), is used. This is the time it takes for the nuclei to release the RF-induced energy and return to a random configuration. The *T1* for protons in fat is much shorter than that for protons in water. This contrast can be maximized by adjusting the time interval of the RF pulse and the time to detect or echo (TE) the induced signal. The total process is often referred to as a pulse sequence or spin-echo sequence. An alternate approach, which also is based on the differences in *T1* between adipose and lean tissues, is called inversion recovery. However, the time required for this method compared with the spin-echo method is much longer; hence, it is rarely used (68, 122, 283, 308).

Depending on the pulse sequence used, the time needed for an abdominal image can take 8–10 min or more, although recent technological advances may have reduced this time to ~30 s/slice (68, 124, 261, 262). For a whole body measurement, a series of multiple scans along the length of the body is needed, which may require the subject to be in the magnet's bore for 30 min or longer. To reduce artifacts introduced by movement, the subject is asked to hold his or her breath for each of the abdominal slices. The relative distribution of total body fat along the length of the body and its visceral component is shown in Figure 6 for a total body MRI scan. Cross-sectional abdominal images obtained with MRI, as shown in Figure 7, allow for separation of the subcutaneous adipose tissue (SAT) from the visceral adipose tissue (VAT) compartment. Several studies have examined the relationship between the VAT and SAT compartments for adults and children (26, 176, 262, 264, 265, 349). Equations (see Table 8) have been developed for the calculation of the VAT or SAT area based on anthropometric measurements, e.g., waist circumference or skinfolds. Although these equations may predict the average VAT for a population, they have limited accuracy for the individual. Several excellent reviews of the practical aspects of the MRI measurement have been presented previ-

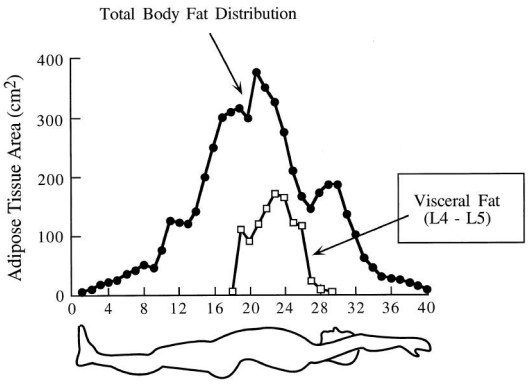

FIG. 6. Distribution of total body fat and visceral fat in an adult, nonobese male obtained using magnetic resonance imaging. [Modified from Despres et al. (68).]

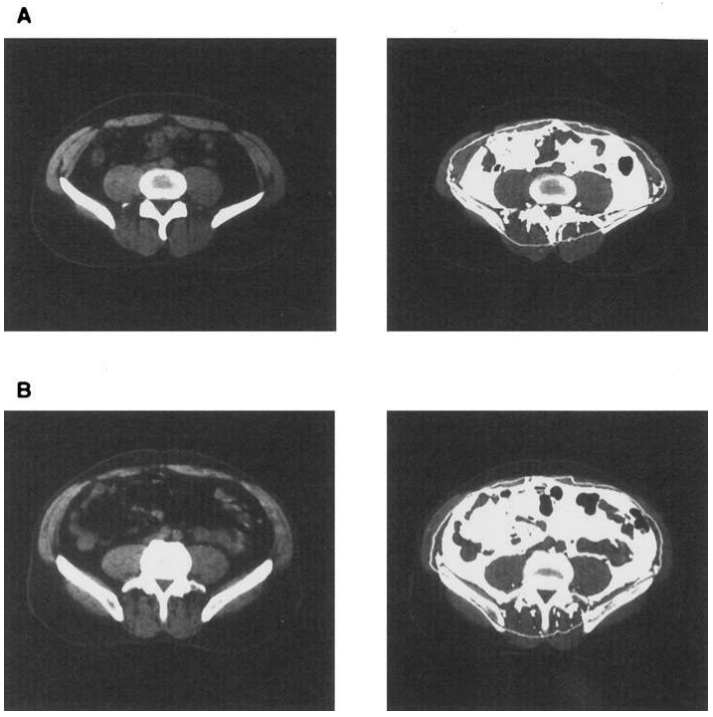

FIG. 7. Cross-sectional images of the abdomen obtained by computed tomography for a young man (*A*) and a middle-aged male (*B*), both with the same total body fat mass. [Modified from Despres et al. (68).]

ously (176, 322), and Smith and Zachwieja (294) recently summarized their use in intervention strategies focused on reduction of VAT.

Animal models and human cadaver studies have been used to verify the accuracy of the estimates of adipose tissue mass and its anatomical distribution (1, 101, 123, 217). Abdominal subcutaneous adipose tissue and visceral adipose tissue, both its intraperitoneal and retroperitonal deposits, were dissected in three human cadavers. Their weights agreed with the MRI estimates with a mean difference of ~6% or 0.08 kg. Similar agreement was obtained for the lean tissues (68).

A significant advantage of MRI for body composition studies is its potential for monitoring changes in the VAT and SAT compartments separately, information which is presently not available with any alternate in vivo techniques except for CT. For example, the relative contributions of each subcompartment to the total abdominal adipose tissue mass have been examined in weight loss programs with and without exercise and/or drug therapies (26, 131, 199, 263, 265). Undoubtedly, MRI will play a vital role in helping to identify individuals at increased risk for a variety of clinical conditions. Recently, the observation of a significant increase of a lipodystrophy-like syndrome in human immunodeficience virus-positive subjects has been confirmed using MRI examinations (40, 152, 202, 330). In these patients, there is a significant loss of fat from the extremities or SAT mass, with an increase in visceral fat deposits. The MRI-derived estimates for abdominal SAT and VAT will serve as a reference measure of adiposity for testing the efficacy of future therapies for obesity.

B. Computed Tomography

This tomographic technique uses X-rays that are collimated to provide a fan-shaped beam that is passed through the body, while an array of detectors is positioned on the opposite side of the subject to detect the transmitted radiation. The X-ray source and detector assembly are rotated as a single unit around the subject covering a full 360° arc. Alternately, some instruments have a full circle of detectors, and only the X-ray source is rotated. At each degree of rotation, the transmitted intensity is recorded for each detector, providing information about the internal structures along that beam path. Many reconstruction algorithms have been de-

TABLE 8. *Relationships between total body fat, abdominal fat, visceral, and subcutaneous fat and anthropometric indexes*

	n	R^2	Reference No.
Adult males (n = 89)			
TBF = 0.05234AAT + 2.8788	89	0.92	68
VAT = 0.0845(WC × HC) + 5.12%fat − 13.715	61	0.73	165
SAT = 3.136WC + 3.663%fat − 237.539		0.81	
VAT = 2.125Age + 2.8343WC − 225.39	110	0.74	68
VAT = 1.05Age + 3.03WC + 4.68BMI − 350	66	0.76	283
SAT = 0.69Age + 3.88WC + 8.83BMI − 413		0.74	
Adult females			
TBF = 0.0593AAT + 1.6589	75	0.97	68
VAT = 1.4Age − 1.6Wt + 2.6HC + 11.4SD − 283	99	0.75	10
VAT = 23.4AFM + 36.6LSSF + 508.2WHR − 503	25	0.91	303
VAT = 4.76SD + 0.76Age + 1.73WC + 0.74PFP − 211.2		0.81	320
Children (n = 101)			
White VAT = 0.23 × SAT + 13	36	0.75	253
Black VAT = 0.17 × SAT + 11	65	0.70	

TBF, total body fat (kg); AAT, abdominal adipose tissue area (cm^2); VAT, visceral adipose tissue area (cm^2); SAT, subcutaneous adipose fat area (cm^2); BMI, body mass index (kg/m^2); WC, waist circumference; SD, sagittal diameter minus subcutaneous fat thickness; %fat, percentage body fat; HC, hip circumference; AFM, abdominal fat mass (by dual-energy X-ray absorptiometry); LSSF, log(sum of skinfolds); WHR, waist-to-hip ratio.

vised to process the cumulative data to produce a cross-sectional image of the body region scanned (68, 147, 260). This basic anatomical image is similar to that obtained using MRI, except it contains additional information for the tissue's true density at each pixel. This information coupled with the anatomical location of the pixel within the image can be used to identify it as adipose, muscle, skin, viscera, or bone tissue. Reconstruction of total body mass and separate organ masses based on scans along the length of the body at 10-cm intervals has been shown to have excellent accuracy (<1% error) and precision (<1%) (266, 292). These reconstructed CT images, and those for MRI, can be assigned to level 4 or tissue systems level of the multicompartment model. The CT images can also be used to separate the total adipose tissue mass into its subcutaneous and visceral components, or the lean tissues into skeletal muscle and visceral or organ mass. Likewise, bone can be identified as cortical or trabecular in nature on the basis of density (61, 182, 196, 224, 273). It has also been shown that CT provides a more accurate determination of visceral adipose tissue than MRI (68, 283) and that the scan times for CT are shorter than for MRI. Unfortunately, the one major disadvantage with CT is the radiation dose required per slice for imaging. However, if the pixel resolution required for routine CT scans (mainly used for detection of tumors) can be relaxed, then the dose can be significantly reduced. Preliminary studies have shown that a 10-scan image of the trunk region can be obtained with an effective dose <0.3 mSv, which is about 1/25 that of a routine clinical CT scan (300). A further substantial reduction in dose, perhaps to a range comparable with fan-beam DXA, may be possible if the pixel resolution can also be reduced.

IX. REFERENCE BODY COMPOSITION DATA

As noted in section I, limited whole body cadaver data are available for humans (105, 116, 118, 119, 130, 157, 164, 223, 342–344). However, several models have been developed to describe human body composition over the full life span: Reference Fetus (352), Reference Infant (111, 297), Reference Children (112), Reference Adolescents (140, 141), and Reference Man (79, 296) and Woman (79). In addition, the comprehensive works of Cheek (42) and Forbes (114) describe body composition during human growth. Collectively, these studies coupled with the work of Moore et al. (221) provide a cornerstone of human body composition research at the elemental, cellular, and tissue levels.

Since these pioneering efforts, a number of newer or more sensitive techniques have been developed that have allowed us to reexamine many of these relationships in more detail and to determine the degree of biological variability seen in the healthy general population with regard to gender, ethnicity, age, and sexual maturation. In this section, a summary of some of the types of changes reported in body composition across the human life span are presented. These examples could not be all inclusive and do not represent a meta-analysis of the data, but serve to illustrate the scope of information that is known. References to additional publications are provided for each age group.

A. Infants

The body composition of the neonate has recently been reviewed (82). During this period of rapid growth, substantial changes in normal body composition will occur and can appear contradictory with the stable composition normally observed for adults (111, 297, 352). The mineral, protein, water, and lipid contents of the body increase with age during early life, each at markedly different rates (see Fig. 8). The nonlinear elemental growth patterns for neonates are described by the equations given in Table 9. The DXA measurements have also been used to examine the body composition of term and preterm infants during the first year of life (32, 166–169, 180, 240, 271, 321, 338, 339). There is also a significant

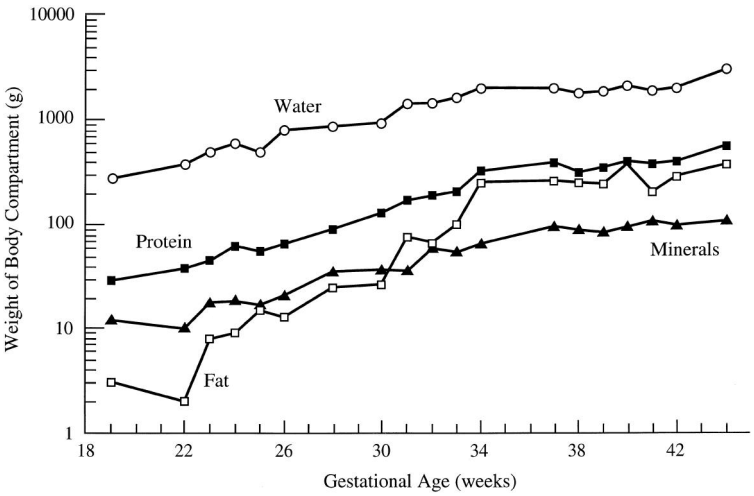

FIG. 8. Changes in human body composition during fetal development and early life. These data often serve as a reference standard for assessing growth in the preterm infant. [Modified from Ellis (82).]

redistribution of body water between its extracellular and intracellular fluid volumes during early life (112).

Limited body composition data exist for children in the toddler years (age range, 1–4 yr). This may be due in part to measurement difficulties, such as insufficient cooperation from the children during the time needed to perform the procedures. Also, there are concerns about the accuracy of some instruments' calibrations for these body sizes (166, 167). In general, it is assumed that the relative bone, lean tissue, and fat proportions that make up the body weight remain unchanged for the infant after an age of 2 yr; that is, during this period of steady growth, there are increases in the various composition compartment such that there is no change in the overall compositional makeup of the body.

B. Children

There is a relatively large number of studies, mainly those using DXA and/or BIA techniques, that have reported body composition values for school-aged children (27, 66, 81, 83, 104, 110, 133, 170, 174, 198, 218, 219, 231). In addition, the 4-C UWW model has also be used to describe body composition in children (340), and there are the classic Reference Child and Reference Adolescent models (112, 140, 141). Only a few of these studies have examined the full age (4–18 yr) for growth, whereas most have focused on narrower age groups, or only one gender, and rarely on ethnic differences (2). A typical summary of body composition data, obtained using total body DXA measurements in a cross-sectional multiethnic study, are presented in Table 10 (81, 83). Similar growth patterns have been reported for other pediatric studies around the world; a comparison of some of these is provided in Figure 9 for girls and in Figure 10 for boys. In some studies, prediction equations for body composition in children, based on the anthropometric parameters of gender, age, weight, and height, have been provided; one set of equations is listed in Table 11 (81, 83, 136, 137, 336).

TABLE 9. *Elemental composition of the neonate as a function of body weight (cadaver studies)*

	Neutron Activation Analysis*		Chemical Cadaver Analysis†		Chemical Cadaver Analysis‡	
Total Body Content	*a*	*b*	*a*	*b*	*a*	*b*
Ca, g	0.00226	1.148	0.00117	1.241	0.00109	1.244
P, g	0.00412	0.996	0.00125	1.164	0.00197	1.109
Na, meq	0.162	0.902	0.362	0.806		
Cl, meq	0.183	0.847	0.284	0.784		
K, meq	0.0716	0.906	0.0449	0.989	0.00327§	1.194§

Elemental content = $a \times Wt^b$, where Wt is body weight (g). *Nutritionally adequate mothers, live births, survival 1–10 days (see Ref. 82). †Summary of literature data for infant cadavers (see Ref. 114). ‡Infants of malnourished mothers (see Ref. 9). §Values are for calculation of total body nitrogen (g).

TABLE 10. *Example of total body composition values for children obtained using DXA technology*

Age Group, yr	BMC, g	Lean Tissue Mass, kg	Fat Mass, kg	%Fat
		Males		
White/European-American (n = 145)				
3–5	423 ± 94	13.25 ± 1.29	2.92 ± 0.44	17.6 ± 2.0
5–9	793 ± 232	20.42 ± 3.95	4.84 ± 3.83	17.1 ± 6.5
10–14	1,655 ± 496	37.74 ± 9.49	12.10 ± 8.41	22.2 ± 10.3
15–18	2,545 ± 430	53.58 ± 7.25	10.26 ± 6.29	14.8 ± 7.0
Black/African-American (n = 78)				
3–5	456 ± 106	14.70 ± 2.22	2.43 ± 0.71	13.7 ± 3.0
5–9	900 ± 195	22.54 ± 3.89	5.20 ± 4.53	16.7 ± 9.4
10–14	2,038 ± 633	45.73 ± 13.4	12.54 ± 10.57	19.2 ± 9.7
15–18	3,181 ± 440	65.51 ± 8.04	14.43 ± 10.30	16.7 ± 10.5
Hispanic/Mexican-American (n = 74)				
3–5	403 ± 63	12.10 ± 1.27	3.28 ± 1.22	20.4 ± 4.8
5–9	827 ± 192	21.42 ± 3.71	7.38 ± 3.38	23.9 ± 6.9
10–14	1,724 ± 475	39.48 ± 9.38	14.81 ± 6.99	26.0 ± 10.3
15–18	2,545 ± 334	53.57 ± 5.99	12.06 ± 7.96	16.6 ± 7.2
		Females		
White/European-American (n = 143)				
3–5	447 ± 93	13.3 ± 1.4	3.5 ± 1.1	20.2 ± 4.7
6–8	528 ± 136	16.5 ± 2.4	5.0 ± 2.2	21.9 ± 5.5
9–11	1,057 ± 246	24.5 ± 4.0	8.8 ± 4.4	24.5 ± 7.8
12–14	1,581 ± 350	33.3 ± 4.9	15.2 ± 7.7	28.9 ± 7.7
15–17	1,967 ± 269	37.9 ± 4.2	15.3 ± 5.3	27.2 ± 5.8
Black/African-American (n = 106)				
3–5	430 ± 187	12.8 ± 3.3	3.8 ± 2.3	21.1 ± 5.9
6–8	844 ± 272	20.2 ± 3.5	7.2 ± 4.9	23.4 ± 8.4
9–11	1,330 ± 325	31.1 ± 5.9	13.3 ± 7.0	27.4 ± 9.0
12–14	1,876 ± 412	36.7 ± 5.7	17.6 ± 9.9	29.5 ± 8.8
15–17	2,148 ± 441	40.6 ± 8.9	21.9 ± 13.8	31.6 ± 9.3
Hispanic/Mexican-American (n = 42)				
3–5	413 ± 92	12.7 ± 2.8	4.6 ± 3.5	23.7 ± 10.2
6–8	626 ± 66	16.4 ± 1.9	6.3 ± 3.3	25.6 ± 7.7
9–11	1,119 ± 417	24.8 ± 5.7	12.1 ± 6.2	30.4 ± 7.3
12–14	1,584 ± 196	34.8 ± 4.1	17.7 ± 9.2	31.2 ± 10.0
15–17	2,108 ± 355	40.3 ± 6.9	26.7 ± 10.5	37.5 ± 6.0

Values are means ± SD. BMC, bone mineral content; %Fat = 100 × Fat/Wt_{DXA}, where DXA is dual-energy X-ray absorptiometry and Wt is weight. Measurements were obtained with Hologic QDR-2000 instrument (see Refs. 81, 83).

Data in children on the relationship between body composition and vitamin D receptor gene classification are emerging in an effort to find an early biomarker for increased risk of osteoporosis in later life (7).

Most of the total body elemental data reported for children have been for TBK (35, 42, 113, 197, 228, 245). Limited data for TBN and TBCa in children have also been reported (4, 17–19, 93, 268).

C. Adults

Most elemental body composition reference data (level 1 model) for adults have been obtained using in vivo neutron activation analysis and whole body counting. Although several research centers have contributed to this database (44, 59, 148, 151, 247, 248, 302), much of the original data were obtained from one research laboratory (34, 55–59, 78, 85, 97, 161). An example of the elemental composition data for adults, ages 20–80 yr, is presented in Table 12. Similar studies in adults are still in progress (151, 247, 248) and are focused, in part, on more precisely defining the range of normal variability with aging for each gender, differences among ethnic groups, and extension of these measurements beyond those of octogenarians (R. N. Pierson, Jr., personal communication).

It should be noted that each of the manufacturers of DXA instruments maintains their own reference database for BMC and BMD as a function of age for total body, lumbar spine, femur, and forearm measurements. Several investigators have recently questioned the general applicability of using only age-specific references without consideration of anthropometric, ethnic, or environmental differences (134, 193, 226, 236, 238, 289). As yet, none of the manufacturers has established a reference BMC or BMD range that also includes effects attributed to differences in height. Likewise, no reference ranges for the lean tissue values, fat mass, or percent fat for adults have been proposed. Some of this may be due to the problem of nonuniformity in calibration among the manufactures as the estimates for the composition of the bone and soft

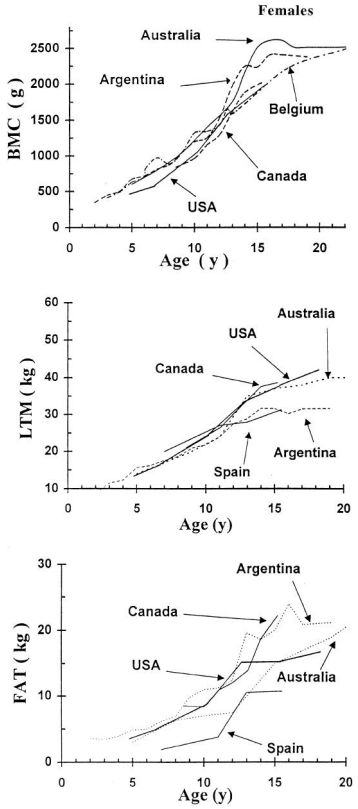

FIG. 9. Comparison of changes in bone mineral content (BMC), lean tissue mass (LTM), and fat mass (Fat) for young females in various countries. [Modified from Ellis et al. (83).]

tissues (lean and fat masses) appear dependent on the choice of instrument and software (92–94, 314–318).

X. MEASUREMENT OF CHANGES IN BODY COMPOSITION

If body composition measurements are obtained only once for an individual, then the most common use is for the assessment of that person's status relative to a reference population. The individual's body composition value can be expressed as a percentage of the expected or predicted normal value, usually after adjusting for variations attributed to gender, ethnicity, age, and indexes of body weight and height (54, 84, 86, 89, 100). An alternate choice is to provide a z-score rating compared with age- and gender-matched reference populations. For this application, the accuracy of the body composition measurement is important, especially if a clinical intervention is to be considered.

When longitudinal measurements are obtained, then changes in body composition can also be assessed. For this application, the absolute accuracy of the measurement is less important because the ability to detect a statistically significant change is more dependent on the precision of the measurement. The relationship between the minimal detectable change (MDC) for an individual and the precision (P) of the measurement, when both are expressed as percents, is %MDC $\cong 2.83 \times$ %P, at a 5% significance level. The precision errors reported for the

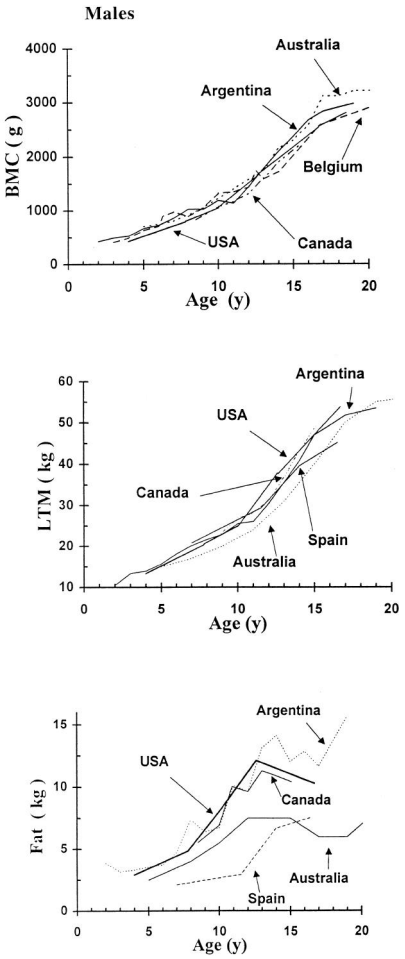

FIG. 10. Comparison of changes in bone mineral content (BMC), lean tissue mass (LTM), and fat mass (Fat) for young males in various countries. [Modified from Ellis (81).]

TABLE 11. *Prediction equations for estimating average body composition in children based on age, weight, and height*

	R^2	SEE	%CV
White (European-American)			
Boys			
BMC = 23.6 Wt + 75.5 age − 416.5	0.86	216 g	15.8
LTM = 0.439 Wt + 1.52 age − 2.76	0.91	3.37 kg	9.1
Fat = 0.534 Wt − 1.59 age + 3.03	0.57	3.56 kg	31.7
Girls			
BMC = 4.38 × Ht + 18.6 × Wt + 59.1 × age − 753	0.86	160 g	11.3
Lean = 0.101 × Ht + 0.346 × Wt + 0.559 × age − 6.93	0.93	1.73 kg	5.6
Fat = 0.642 × Wt − 0.120 × Ht − 0.606 × age + 8.98	0.86	1.09 kg	9.7
Black (African-American)			
Boys			
BMC = 21.3 Wt + 106.3 age − 525.3	0.91	215 g	11.0
LTM = 0.363 Ht + 0.388 Wt − 34.2	0.92	3.94 kg	8.9
Fat = 0.594 Wt − 0.381 Ht + 36.0	0.62	4.29 kg	36.1
Girls			
BMC = 7.22 × Ht + 17.2 × Wt + 49.8 × age − 919	0.87	179 g	10.7
Lean = 0.143 × Ht + 0.336 × Wt + 0.301 × age − 8.96	0.91	2.37 kg	6.8
Fat = 0.653 × Wt − 0.163 × Ht − 0.298 × age + 10.7	0.91	2.45 kg	16.7
Hispanic (Mexican-American)			
Boys			
BMC = 16.9 Wt + 102.3 age − 437.2	0.86	212 g	12.5
LTM = 0.424 Wt + 1.56 age − 2.98	0.91	3.34 kg	8.7
Fat = 0.591 Wt − 1.82 age + 3.36	0.55	3.71 kg	25.7
Girls			
BMC = 8.04 × Ht + 14.4 × Wt + 40.9 × age − 928	0.85	179 g	12.2
Lean = 0.212 × Ht + 0.287 × Wt + 0.011 × age − 15.1	0.92	2.22 kg	6.9
Fat = 0.677 × Wt − 0.217 × Ht + 15.5	0.90	2.44 kg	15.1
BMC vs. LTM			
Boys BMC(g) = 51.25 LTM(kg) − 258.8	0.94	144 g	8.7
Girls BMC(g) = 60.25 × lean(kg) − 379.5	0.87	166 g	9.9

Stepwise multiple-regression analysis [potential prediction variables: age (yr), weight (Wt; kg), and height (Ht; cm)]. R, correlation coefficient; SEE, standard error of estimate; %CV, coefficient of variance, expressed as a percentage, at mean age of 12 yr; BMC, bone mineral content; LTM, lean tissue mass. Relationship between BMC and LTM was independent of race. For details, see Refs. 81, 83.

various body composition measurement techniques discussed in the previous sections of this review are summarized in Table 13. The precision errors typically range from 1 to 5%, with the exception of the visceral fat area or volume estimates that are of the order of 5% or higher. Estimates for the accuracy errors for each of the methods are also included in Table 13. These tend to be higher than the precision errors reflecting the degree of difficulty associated with a calibration that must account for the full range of biological variations, such as body size and proportions, that often affect the parameters being measured; that is, the measurement techniques can have good reproducibility, but the estimated quantity (mass, volume, area, or density) for a specific body composition compartment for the individual is less certain. The estimated MDC values for an adult (based on the body composition estimates for the ICRP-23 Reference Man model, Ref. 296) are also provided in Table 13, expressed in both absolute units and as a percent. The MDC values listed in Table 13 are those required for an individual for there to be a statistically significance change. It is evident that, even with good precision, a substantial change for the individual must occur to be of statistical significance. These changes can often occur with or without additional indexes of an altered quality of life. For example, a healthy young adult would not be expected to have a 4–5% change in TBCa or BMC, whereas this could occur in a relatively short time interval for an otherwise healthy older woman (57, 78). For example, during menopause, most women will experience a more rapid rate of bone loss and the %MDC for BMC or TBCa for an individual may in fact be exceeded, thus the interest in using these measurements for screening women to identify those with increased risk for osteoporosis. Likewise, the %MDC values are also useful when assessing changes in the lean tissues or fat mass associated with many diseases and their treatments.

Detection of a statistically significant change for the individual can often require long time intervals between the measurements, especially if the changes are occurring at relative slow rates. However, unlike the clinical setting where body composition measurements are used to assess the status of an individual patient, the research applications of these measurements are usually focused on assessing the efficacy of a specific therapy or treatment regime for a group of subjects. In this case, the statistical ability to identify a significant change in body composition is dependent not only on the measurement precision, but also the biological variability of the body composition parameter in the research population and the sample size of the study group. If $\%MDC_g$ denotes the minimal detectable percentage change for a group of n subjects with a biological variation denoted as $\%SD_{biol}$, and %P is the measurement precision, then $\%MDC_g \cong 2.83 \times n^{-1/2} \times (\%P^2 + \%SD_{biol}^2)^{1/2}$, at a 5% significance level (143, 144). For a given measurement precision, an increase in the sample size improves the statistical ability to detect a smaller change as significant. Alternately, as the measurement precision worsens or the SD_{biol} for the population increases, larger sample sizes are needed to detect the same level of change.

Thus, when designing a research protocol that relies on detection of significant changes in body composition as an end point, the relationship presented above for $\%MDC_g$ needs to be considered. Because the measurement precision (determined by the choice of measurement technique) and biological variability (determined by selection of study population) are basically fixed parameters, this leaves the researcher with determining the

TABLE 12. *Mean body composition estimates for adults*

Age Group, yr	BMI, kg/m^2	TBW, l	TBPr, kg	BCM, kg	OsMin, kg	ICW, l	ECW, l	ECW/TBW	FFM, kg
				Males					
20–29	24.1	45.4	12.6	34.5	2.97	27.6	17.8	0.39	62.6
30–39	24.3	39.7	11.3	30.9	2.76	24.7	14.9	0.38	55.7
40–49	25.2	43.2	11.4	31.4	2.72	25.1	18.1	0.42	57.7
50–59	26.5	43.7	11.4	29.1	2.64	23.3	20.4	0.47	56.5
60–69	25.8	39.7	10.6	28.9	2.66	23.1	16.5	0.42	53.3
70–79	26.5	41.6	9.7	24.9	2.66	19.9	21.6	0.52	50.2
				Females					
20–29	22.1	31.1	9.1	21.1	2.25	16.9	14.2	0.46	43.4
30–39	22.7	32.0	8.8	22.2	2.06	17.8	14.2	0.44	44.1
40–49	24.9	30.5	8.4	20.2	2.12	16.2	14.3	0.47	41.4
50–59	25.6	30.9	7.8	20.0	1.96	16.0	14.9	0.48	40.5
60–69	25.4	27.6	7.2	16.9	1.74	13.5	14.0	0.51	35.8
70–79	24.5	25.7	6.8	15.6	1.59	12.5	13.3	0.52	33.5

Values are for Caucasian males and females in the United States. Estimates are based on tritium dilution, ^{40}K counting, and neutron activation analysis measurements (see Refs. 55–59, 78, 178). TBW, total body water; TBPr, total body protein; BCM, body cell mass; OsMin, bone mineral mass; ICW, intracellular water; ECW, extracellular water; FFM, fat-free mass.

appropriate sample size to detect a specific percentage change. A second consideration of equal importance is the selection of an appropriate time interval between measurements. This is crucial, for if the time interval is too short, then it may not be physiologically possible to achieve the targeted percentage change. Alternately, if the time period between measurements is relatively long, then the normal physiological changes in body composition (for example, growth for children or aging for older adults) must also be taken into consideration. To control for these latter concerns, it is advised that whenever possible control or untreated groups matched with the treatment group should also be examined.

TABLE 13. *Precision, accuracy, and detectable changes for an individual using various body composition measurement techniques*

Body Composition Compartment (Method)	Measurement		Minimum Detectable Change for an Individual
	Precision,* %	Accuracy,† %	
TBK (^{40}K counting)	1–3	5	150 meq (4%)
TBW (D_2O dilution)	1–2	2	2 liters (5%)
ECW (Br dilution)	2–3	2–4	2 liters (10%)
TBN (Prompt-γ)	2–4	3	130 g (7%)
TBCa (Delayed-γ)	1–2	5	55 g (5%)
FFM (UWW/ADP)	1–2	2–3‡	4 kg (6%)
FFM (BIA/BIS)	1–2		2–4 kg (7%)
DXA			
BMC (g)	1–2	2–10§	160 g (4%)
LTM (kg)	2–3	5	4 kg (7%)
Fat (kg)	3–4	5–10	1 kg (10%)
VAT (MRI/CT)	5–10		

TBK, total body potassium; TBW, total body water; ECW, extracellular water volume; TBN, total body nitrogen; TBCa, total body calcium; FFM, fat-free mass; DXA, dual-energy X-ray absorptiometry; VAT, visceral adipose tissue; BMC, bone mineral content; LTM, lean tissue mass; MRI, magnetic resonance imaging; CT, computed tomography. Estimates of minimum detectable change for an individual were based on ICRP-23 Reference Man model. *Reproducibility for repeat measurements. †Accuracy error for absolute mass or volume estimate. ‡Dependent on choice of model used. §Error tends to increase if specific bone site is measured.

XI. SUMMARY

In vivo methods continue to be developed for use in human body composition research. Many of these technological advances should provide accurate and precise assessment not only of adults, but also for infants and children. It is now becoming evident that many diseases that become manifest in adulthood may have their origins in childhood. Thus one area of further research on the development of methods can be expected to focus on children, especially applications in longitudinal studies. Likewise, the adult population is aging, and an increasing percentage of the elderly is surpassing the average life expectancy of the past generations. With advancing age there are changes in body composition that may impact on the quality of life. Areas of future investigation for adults will focus not only on the prevention and treatment of osteoporosis, but also that of sarcopenia with aging. However, the most significant health issue that will probably be addressed at the start of the third millennium is that of human obesity.

It would be impossible to provide an all-inclusive bibliography of body composition in a single review (for example, a Medline search of bone mineral density and children alone yielded >500 references). However, current and representative references, as well as several classic citations, from the many research groups actively involved in body composition measurements are provided here. In particular, the information contained in the international body composition conference series (6, 86, 99, 351), the more detailed description of the various meth-

ods (259, 302), and a summary of the five-level model (333, 335) should provide a strong foundation for both the novice and experienced body compositionist.

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